REMARKS

I. Status of Claims

Claims 1-30 are pending in this application. Applicant notes with appreciation the Examiner's withdrawal of the rejection under 35 U.S.C. § 103 of claims 3-6, 8, 9, 12-19, 22-25, and 27-29 over Olsen in view of Metra. (Office Action, pg. 5.)

II. Rejections under 35 U.S.C. §§ 112, First Paragraph

Claims 1-6, 14, 15, 17, 18, 22, 23, and 26-30 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. (Office Action, pg. 2.) The Office contends that the recitations of a "maintenance phase of greater than six months" in claims 1, 14, 17, 22, 26, and 27 and "to statistically decrease the risk of mortality caused by congestive heart failure" in claims 12, 15, 18, 23, and 28 are new matter. (*Id.*) Applicant respectfully disagrees and traverses the rejection.[1]

A. THE WRITTEN DESCRIPTION IS DIRECTED TO A SHOWING THAT THE INVENTOR HAD POSSESSION OF THE CLAIMED SUBJECT MATTER

To satisfy the written description requirement, the specification need only "convey clearly to those skilled in the art the information that the applicant has invented

[1] Applicant also does not understand the timing of these rejections, issued for the first time as a new ground of rejection in the Office Action dated May 16, 2007. *See* 37 CFR § 1.104 (b); MPEP § 707.07. The claim recitations referenced in the Office Action were contained in the original preliminary amendment dated November 25, 2003, which included express citations in the '821 patent of exemplary support. Indeed, the claims with these limitations have been previously allowed by the present Examiner. (*E.g.,* October 3, 2006, Notice of Allowability.) If a change in policy or practice by the Office, Art Unit or Examiner is implicated in these continued rejection of the present application and the continued issuance of new grounds of rejections to the previously allowed subject matter, Applicant requests that the policy or practice be explained and included in the Office's response to this Reply.

the specific subject matter later claimed." *See, e.g.*, MPEP § 2163.02; *In re Wertheim*, 541 F.2d 257, 262, 191 U.S.P.Q. 90, 96 (C.C.P.A. 1976); *In re Ruschig*, 379 F.2d 990, 996, 154 U.S.P.Q. 118, 123 (C.C.P.A. 1967). Accordingly, a rejection for lack of written description support requires the Office to provide "reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed." MPEP § 2163(III)(A) (emphasis added). Further, the subject matter of the claim need not be described literally or *in ipsis verbis* in order for the specification to satisfy the description requirement. *See, e.g.*, MPEP § 2163.02; *Cordis Corp. v. Medtronic Ave., Inc.*, 339 F.3d 1352 (Fed. Cir.), *reh'g denied*, 2003 U.S. App. LEXIS 22508 (2003); *In re Lukach*, 442 F.2d 967, 969, 169 U.S.P.Q. 795, 796 (C.C.P.A. 1971).

As discussed below, the present specification provides more than sufficient disclosure to show that the inventors had possession of the claimed subject matter and that a prima facie case of unpatenability has not been presented. Indeed, the Office has offered no "reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed." MPEP § 2163(III)(A) (emphasis added).

B. POSSESSION OF A "MAINTENANCE PERIOD OF GREATER THAN SIX MONTHS"

1. Treatment stages and periods

The specification provides detailed disclosure regarding a three-stage treatment regime, comprising challenge, titration, and maintenance periods. For example, in the '821 patent at column 5, lines 21-35, it is disclosed that:

> Compounds having the above-mentioned dual properties are preferably administered following a **three-stage application scheme**. This scheme is characterized by the fact that incremental dosages of the active ingredient are administered to patients over a certain period of time, until the regular maintenance dosage is received. If this maintenance dosage is defined as the setting value being 100%, it was found that the **application regimen in a first phase should extend for a period of 7-28 days, whereby only 10-30% of the setting dose are administered**. Following this phase, **a second application regimen should follow, wherein a dosage of 20-70% of the setting dose is administered** to the patient for a period of 7-28 days. After termination of this phase, **the third application period follows, wherein the daily complete setting dose (maintenance dose) is administered.** The daily maintenance dose can vary between 10-100 mg of said active ingredient.

(Emphasis added.) The specification further provides that:

> As one of ordinary skill in the art will readily comprehend, the patient should be started on a low dosage regimen of the desired compound of Formula I, particularly carvedilol, and monitored for well-known symptoms of intolerance, e.g., fainting, to such compound. Once the patient is found to tolerate such compound, the patient should be brought slowly and incrementally up to the maintenance dose. **The preferred course of treatment is to start the patient on a dosage regimen with formulations which contain either 3.125 or 6.25 mg of active compound per single unit, preferably given twice daily, for 7-28 days**. The choice of initial dosage most appropriate for the particular patient is determined by the practitioner using well-known medical principles, including, but not limited to, body weight. In the event that the patient exhibits medically acceptable tolerance of the compound for two weeks, **the dosage is doubled at the end of the two weeks and the patient is maintained at the new, higher dosage for an additional period, preferably to two more weeks**, and observed for signs of intolerance. **This course is continued until the patient is brought to a maintenance dose**. The preferred maintenance dose is 25.0 mg of active compound per single unit, preferably given twice daily, for patients having a body weight of up to 85 kg.

('821 patent, col. 5, ll. 40-63 (emphasis added).) A three-stage treatment schedule is summarized as:

> The present invention relates also to method of treatment for decreasing mortality resulting from congestive heart failure in mammals comprising internally administering to said mammal in need thereof an effective amount of carvedilol according to the following schedule:
>
> (a) a pharmaceutical formulation which contains either 3.125 or 6.25 mg carvedilol per single unit for a period of 7-28 days, given once or twice daily.
>
> (b) thereafter a pharmaceutical formulation which contains 12.5 mg carvedilol per single unit for a period of additional 7-28 days, given once or twice daily and
>
> (c) finally a pharmaceutical formulation which contains either 25.0 or 50.0 mg carvedilol per single unit, given once or twice daily as a maintenance dose

('821 patent, col. 6, ll. 1-24). Indeed, the specification further provides details of a clinical study having challenge, titration, and maintenance phases:

> The purpose of the screening period was to quality patients for study entry obtain reproducible baseline measurements, and stratify patients into the appropriate trial based on submaximal exercise testing. During the **challenge period**, patients received low-dose open-label carvedilol (6.25 mg b.i.d.) for two weeks. Patients unable to tolerate this dose did not proceed to randomization. Patients tolerating low-dose carvedilol were then randomized to blinded medication (carvedilol or placebo) with the dose **titrated over several weeks** in the range of 6.25 to 50 mg b.i.d. (or equivalent level of placebo). **The maintenance phase** of each study ranged from six to 12 months, after which patients had the option of receiving open-label carvedilol in an extension study.

('821 patent, col. 7, ll. 46-59.)

Based on the above-quoted excerpts, as well as the specification as a whole, Applicant respectfully submits that a person skilled in the art would have recognized that

the inventors were in possession of a three-stage treatment regime for carvedilol, comprising challenge, titration, and maintenance periods. Further, the Office has provided no reasons or evidence to the contrary. *See* MPEP § 2163(III)(A). Applicant submits that a person of ordinary skill would further have understood the maintenance phase could be an ongoing treatment. In addition to the specific disclosure discussed further below, the very nature of maintenance treatment is an ongoing "treatment regime intended to preserve benefit." (Stedman's Medical Dictionary, 26th Ed. (1995), pg 1054 (Attachment A).)

2. Maintenance period of greater than six months

The Office recognizes that the specification discloses a maintenance phase of greater than six months, specifically stating that in the specification, "[o]n lines 56-58 [of column 7,] the maintenance phase of each study is stated to range from six **to 12 months**." (Office Action, pg. 2 (emphasis added).) Indeed, the very same portion of the specification referenced by the Office further provides the continuation of this final treatment phase without temporal limitation beyond the initial six to 12 months:

> **The maintenance phase** of each study ranged from six to 12 months, **after which patients had the option of receiving open-label carvedilol in an extension study**.

('821 patent, col. 7, ll. 56-59.) Similarly, while time periods of finite duration are provided for the challenge and titration phases, in contrast the maintenance phase is without a limited duration. (*See* '821 patent, col. 5, ll. 21-35, 40-63; col. 6, ll. 1-24.) This evidences that an open ended maintenance phase beyond the specified 6 to 12 months initial duration was contemplated and disclosed by the inventors.

Thus, based on (1) the Office's recognition that the maintenance period of greater than six months is disclosed, (2) the above-quoted excerpt showing possession

of ongoing maintenance treatment beyond the specified initial periods, (3) the specification as a whole and (4) the understanding of these from the perspective of one skilled in the art, Applicant respectfully submits that a person skilled in the art would have recognized that the inventors were in possession of a maintenance phase of greater than six months, and that the Office has not provided any reasons to the contrary. *See* MPEP § 2163(III)(A).

The Office nevertheless contends that "[t]he referenced protocols do not correlate with the recited limitations in each of the present claims with respect to a 'maintenance period.'" (Office Action, pg. 2.) This contention, however, is not understood. To the extent the Office's contention is based on an alleged absence of the claimed phrase from each and every reference to any treatment regime or maintenance phase in the specification, Applicant notes that under the applicable legal standard the subject matter of the later claim need not be described literally or *in ipsis verbis* in order for the specification to satisfy the description requirement. *See, e.g.*, MPEP § 2163.02. As noted above, there is substantial disclosure from which a person skilled in the art would have recognized that the inventors were in possession of a maintenance phase of greater than six months, and that the Office has not provided any reasons or evidence to the contrary. *See* MPEP § 2163(III)(A). Specifically, the Office has not provided any reason why disclosure related to maintenance treatment of greater than six months would not have been understood by one skilled in the art to show that the inventors had possession of this subject matter generally as it relates to treatment with carvedilol to reduce or decrease a risk of mortality.

To the extent this rejection is maintained, Applicant requests a clarification of the Office's position, including (1) a clarification of what is intended by the alleged lack of "correlat[ion]" and (2) the reasons and evidence why, for each of the portions of the specification quoted above, the Office believes that a person skilled in the art would not have recognized that the inventors were in possession of a maintenance phase of greater than six months. Further, to clarify the record for appeal, should the reasons be based on something other than cited references, an affidavit under 37 CFR § 1.104(d)(2), attesting that the rejection is based on facts with the personal knowledge of the Examiner and specifying those facts, is specifically requested.

Reconsideration and withdrawal of the rejection are respectfully requested.

C. POSSESSION OF A METHOD TO "STATISTICALLY DECREASE THE RISK OF MORTALITY CAUSED BY CONGESTIVE HEART FAILURE"

The specification contains repeated and explicit support for statistically decreasing the risk of mortality caused by congestive heart failure. (*E.g.*, '821 patent, col. 3, ll. 49-63 (*E.g.,* "[t]he most surprising observation from the studies in which the instant compounds were used to treat CHF is that said compounds, in particular carvedilol, are able to decrease the mortality resulting from CHF in humans by about 67 percent.").) Indeed, the measure of mortality risk is necessarily statistical due to the nature of the treatment and the measure of mortality in terms of patient deaths. (*E.g.,* '821 patent, col. 7, ll. 38-44 ("Although each trial had its own individual objectives, the overall program objective defined prospectively was evaluation of all-cause mortality. Based upon a projected enrollment of 1100 patients, the program had 90% power to detect a 50% reduction in mortality (two-sided) between carvedilol and placebo,

assuming a mortality rate in the placebo group of 12% over the duration of the trials (α=0.05).")

Applicant respectfully submits that based on the above-cited disclosure, as well as the specification as a whole, the written description requirement has been more than met, as a person skilled in the art would have recognized that the inventors were in possession of a method of decreasing a risk of mortality caused by CHF and that the decrease was, as disclosed and by its very nature, a statistical decrease in risk. *See* MPEP § 2163(III)(A).

There is additional support demonstrating the inventor's possession of the claimed subject matter. For example, the specification discloses in Table 2 ('821 patent, column 2-3) a reduction, based on carvedilol relative to placebo, in mortality risk for all cause mortality of 67%, for Class II CHF of 68%, for Class III-IV CHF of 66%, for ischemic etiology of 67%, and for non-ischemic etiology of 67%. These results are based on a study of 1052 CHF patients, under four different protocols, commonly having a challenge period of 6.25 mg carvedilol b.i.d. for two weeks and dose titration over several weeks in the range of 6.25 to 50 mg b.i.d. (Col. 6, ll.43 - col. 7, ll. 56.) The specification also explains that the titration comprises successive dose doubling until the maintenance dose is reached. (Col. 5, ll. 54-60.) Further, the protocols entailed a maintenance phase for six to 12 months, "after which the patients had the option of receiving open-label carvedilol in an extension study." (Col. 7, ll. 56-65.)

The Office contends that "[t]he specification fails to provide statistical support <u>for each</u> of the claimed methods with respect to dosages and dosing regimens." (Office Action, pg. 3 (emphasis added).) Implicitly, the Office recognizes, therefore, that there

is statistical support for at least some of the claimed methods. Nevertheless, inconsistent with this recognition, the Office has rejected every claim reciting the term "statistically."

Further, as noted above, the nature of the referenced mortality risk reduction as being a statistical reduction is both express and implicit in the nature of the measure of mortality based on patient deaths. Thus, for this additional reason, it is submitted that one skilled in the art would have understood that the inventors were in possession of methods of using carvedilol to statistically decrease the risk of mortality caused by CHF. Again, *in ipsis verbis* support is not required. *E.g.*, MPEP § 2163.02

Should the present rejection be maintained, the Office is requested to clarify which methods it finds supported. Further, to clarify the record for appeal, should the reasons be based on something other than cited references, an affidavit under 37 CFR § 1.104(d)(2), attesting that the rejection is based on facts within the personal knowledge of the Examiner and specifying those facts, is specifically requested.

Reconsideration and withdrawal of the rejection are respectfully requested.

III. Rejection under 35 U.S.C. § 102(a)

Claim 9 was rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Metra (Metra et al., Journal of the American College of Cardiology 24(7), pg. 1678-87 (Dec. 1994)). (Office Action, pg. 3.) Applicant respectfully disagrees and traverses the rejection.

The Office relies on Metra for disclosing "the administration of carvedilol to both reduce [1] heart rate and also [2] mean pulmonary artery and pulmonary wedge

pressure in the short term, and, [3] improve exercise left ventricular systolic function and [4] reduce heart failure symptoms in the long term." (Office Action, pg. 5.) On that basis, the Office concludes that "carvedilol clearly decreases a risk of morality in [CHF] patients." (*Id.*) However, the evidence of record shows, as discussed further below and for the reasons of record, that the treatment of CHF mortality is distinct from the treatment of CHF symptoms and hemodynamics attributed by the Office to Metra. Specifically, based on the evidence of record, Applicant submits that treating to:

(1) reduce heart rate,

(2) reduce pulmonary artery or wedge pressure,

(3) improve exercise function, and/or

(4) reduce heart failure symptoms

would not have been considered treating to decrease a risk of mortality.

Accordingly, Applicant respectfully disagrees that Metra "describe[s] all of the elements of the claims, arranged as in" claim 9. *C.R. Bard, Inc. v. M3 Systems, Inc.*, 157 F.3d 1340, 1349, (Fed. Cir. 1998) ("When the defense of lack of novelty is based on a printed publication that is asserted to describe the same invention, a finding of anticipation requires that the publication describe all of the elements of the claims, arranged as in the patented device."); *see also Merck & Co., Inc. v. Teva Pharmaceuticals USA, Inc.*, 347 F.3d 1367, 1372 (Fed. Cir. 2003) (prior art reference that stated generally that composition might be useful for "pharmaceutical preparations" but did not disclose using the composition for the specific bone therapy of the claimed method did not anticipate that claimed method).

Further, for at least the reason that Metra is directed to the treatment of hemodynamics and symptoms and not mortality, Applicants submit that the Office has not shown how Metra would have "sufficiently describe[d] the claimed invention to have placed the public in possession of it." *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985).

A. THE OFFICE'S CONSTRUCTION OF DECREASING A RISK OF MORALITY IS UNSUPPORTED AND IMPROPER

The rejection under 35 U.S.C. § 102 rests on the Office's interpretation of decreasing a risk of mortality as encompassing symptoms and hemodynamics attributed to the disclosure of Metra. (Office Action, pg. 5.) The Office similarly contends that "reducing the risk of mortality" "mean[s] not only a decrease in the death rate, but also the qualities and conditions of being liable or subject to death." (Office Action, pg. 6; *see also* pg. 10 (*citing* Stedman's Medical Dictionary).)[2]

More specifically, in conjunction with its construction, the Office cites Metra for disclosing:

> the administration of carvedilol to both [1] reduce heart rate and also [2] mean pulmonary artery and pulmonary wedge pressure in the short-term, and, [3] improve exercise left ventricular systolic function and [4] reduce heart failure symptoms in the long-term.

[2] Although Stedman's is cited as support, the Office's definition is not found therein. Instead, the Office's proposed definition appears to be a hybrid of an alternate definition of "mortality," *i.e.,* "The quality or condition of being mortal," and one of the alternate definitions of "mortal," *i.e.,* "Liable or subject to death." The Office has--without cited support and for no reasons stated on the record--ignored Stedman's definition of mortality as "death rate," which is consistent with "reducing the risk of mortality" as used in present application. Likewise, for reasons not stated on the record, the Office has ignored Stedman's definition of "mortal" as "causing death; fatal," which is, again, consistent with the concept of "reducing the risk of mortality" according to the present specification.

(Office Action, pg. 6.)[3] Relying on its definition, the Office contends that because Metra discloses the treatment of these symptoms, Metra therefore discloses the treatment of CHF for reducing the risk of mortality. (*Id.*) That is, the Office is equating the treatment of symptoms and quality of life with the reducing the risk of mortality. However, the Office's interpretation of the claim as encompassing merely improved exercise tolerance and hemodynamic functions (*e.g.* Office Action, pg. 5) is unsupported and improper. Indeed, it is inconsistent with the specification.

Claim language should be construed by the Office as broadly as possible consistent with the specification. *In re Bond*, 910 F.2d 831, 833 (Fed. Cir. 1990); *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997). The Office may not ignore the guidance of the specification to apply a construction inconsistent therewith. *Morris* at 1054 (instructing "it would be unreasonable for the PTO to ignore any interpretive guidance afforded by the applicant's written description"). Indeed, the specification is "the single best guide to the meaning of a [claim] term." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315-17 (Fed. Cir. 2005) (*en banc*). Consistent with this principle, the construction that "most naturally aligns with the patent's description of the invention will be, in the end, the correct construction." *Renishaw PLC v. Marposs Societa' Per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998). Here, however, the Office's modified dictionary-based construction of decreasing the risk of mortality is improperly inconsistent with the

[3] The Office cites to the conclusion in the Abstract of Metra (pg. 1686), but does not address the statement in the conclusion of the paper itself that:

> [p]eak exercise capacity is not significantly affected by either short- or long-term carvedilol administration, whereas a significant improvement in clinical symptoms, quality of life and submaximal exercise duration was detected after long-term therapy. No baseline variables permit prediction of the response to therapy.

specification and as well as the art discussed therein. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 981 (Fed. Cir. 1995), *aff'd.* 517 U.S. 370 (1996) (Dictionaries may not be used "for the purpose of varying or contradicting the terms of the claims."); *Cook Biotech Inc. v. Acell, Inc.*, 460 F.3d 1365, 1378 n. 7 (Fed. Cir. 2006).

1. The Office's Construction is Inconsistent with the Background of the Invention

The specification cites, by way of background, Applefeld, M.M., (1986) Am. J. Med., 80, Suppl. 2B, 73-77, for teaching that CHF results in "excess mortality," and goes on to explain that "therapeutic agents that would decrease the mortality resulting from CHF in patients suffering therefrom are highly desirable." ('821 patent, col. 1, ll. 44-46.) In contrast to the Office's modified dictionary-based construction, Applefeld distinguishes between quality of life, on the one hand, and mortality rate, on the other hand. For instance, Applefeld comments that CHF results in both "[1] an impaired quality of life and [2] significant morality rate." (Exhibit B, Applefeld, pg. 73.)

It is inconsistent with the specification and usage of terms in the art for the Office to define "decreasing a risk of mortality" or "reducing the risk of mortality" to encompass the mere treatment of symptoms and quality of life factors attributed to Metra. (Office Action, pg. 5.) The Office's construction is, therefore, improper for at least this reason. *Bond* at 833; *Morris* at 1054.

2. The Office's Proposed Construction is Inconsistent with the Detailed Description of the Invention

Describing the unexpected results of the present invention, the specification states that "the most surprising observation from the studies in which the instant compounds were used to treat CHF is that said compounds, in particular carvedilol, are able to decrease the mortality resulting from CHF in humans by about 67 percent."

('821 patent, col. 3, ll. 59-63.) The "result is surprising since two recent mortality studies using the β-blockers metoprolol and bisoprolol in the treatment of CHF showed no difference in mortality between drug-treated patients and placebo-treated patients." ('821 patent, col. 3, ll. 64 - col. 4, ll. 4 (*citing* the Waagstein and CIBIS studies described below) (emphasis added).)

Applicant's express statement that two studies showed "no difference in mortality" is particularly instructive regarding the meaning of "mortality" in the art and context of the specification. Again, and as discussed further below with respect to each of the cited references, it shows that the Office's attempt to include the treatment of symptoms and qualify of life factors within the meaning of "decreasing a risk of mortality" or "reducing the risk of mortality" is improper and inconsistent with the specification and the art.

A) WAAGSTEIN USES "MORTALITY" TO CONNOTE NUMBER OF DEATHS, DISTINCT FROM HEMODYNAMIC AND QUALITY OF LIFE FACTORS

The Waagstein study "aimed to find out whether metoprolol improves overall survival and morbidity" in the treatment of idiopathic dilated cardiomyopathy. (Exhibit C, Waagstein, The Lancet, 342 (1993), pg. 1441.) To this end, Waagstein compared total mortality (number of deaths) between the placebo group and metoprolol group, and concluded that "metoprolol had no effect on all-cause mortality." (*Id.* at Table 2 and 1445.) Thus, as properly characterized in the present specification, metoprolol "showed no difference in mortality between drug-treated patients and placebo-treated patients." ('821 patent, col. 3, ll. 64 - col. 4, ll. 4 (emphasis added).)

In contrast to the absence of any benefit on death rate, Waagstein concluded that myocardial function and quality of life of the metoprolol patients improved

significantly. (*Id.* at 1443-4.) Specifically, Waagstein reports that in the metoprolol groups there was:

(1) an increase in ejection fraction,

(2) improvement in reported quality of life,

(3) improvement in exercise capacity and time at 12 months,

(4) decrease in heart rate, and

(5) decrease in pulmonary wedge pressure.

(*Id.* at 1443-4.)

The Office's construction of the claims to encompass the results of improved clinical symptoms, quality of life and submaximal exercise duration according to Metra (Office Action, pg. 5), is, therefore, inconsistent with the specification's reference to Waagstein as "show[ing] no difference in mortality between drug-treated patients and placebo-treated patients." ('821 patent, col. 3, ll. 64 - col. 4, ll. 4 (emphasis added).) Indeed, the non-mortality effects of metoprolol according to Waagstein appear to include all of the effects attributed by the Office to Metra as showing a decrease in a risk of mortality. (*E.g.,* Office Action, pg. 5 (*citing* Metra for "the administration of carvedilol to both [1] reduce heart rate and also [2] mean pulmonary artery and pulmonary wedge pressure in the short-term, and, [3] improve exercise left ventricular systolic function and [4] reduce heart failure symptoms in the long-term.").) This further evidences the impropriety of the Office's construction. *Bond* at 833; *Morris* at 1054.

B) CIBIS REFERENCE CITED IN THE SPECIFICATION USES "MORTALITY" TO CONNOTE NUMBER OF DEATHS DISTINCT FROM HEART RATE AND FUNCTIONAL STATUS

The Cardiac Insufficiency Bisoprolol Study (CIBIS) evaluated the impact of treatment with bisoprolol on mortality in patients with heart failure of various etiologies, and distinguished (1) a reduction in mortality from (2) the treatment of symptoms. (The Cardiac Insufficiency Bisoprolol Study (CIBIS), Circulation, 90, No. 4 (1994), pg. 1765 (Exhibit D).) By comparing the number of deaths between the placebo and bisoprolol groups, the CIBIS concluded that bisoprolol "did not significantly reduce mortality." (*See id.* at 1767 and Table 2 (emphasis added).) Thus, as properly characterized in the present specification, bisoprolol "showed no difference in mortality between drug-treated patients and placebo-treated patients." ('821 patent, col. 3, ll. 64 - col. 4, ll. 4 (emphasis added).)

As was the case with metoprolol, however, CIBIS reports that "the functional status of patients was significantly improved by bisoprolol compared with the placebo." (CIBIS, pg. 1771 (emphasis added).) Further, CIBIS reports a mean heart rate reduction of 19% with bisoprolol without any significant change in the placebo group. (CIBIS, pg. 1767, Fig. 1.) In other words, although there was not a statistically significant reduction in mortality, there was an improvement in the quality of life and reduction in heart rate among the patients taking bisoprolol.

Again, it appears that the Office's misconstruction of the claims to encompass the results attributed to Metra is inconsistent with the "mortality" as used in the present specification and the CIBIS reference cited and characterized therein. The Office's construction is, therefore, improper for at least this additional reason. *Bond* at 833; *Morris* at 1054.

3. The Office's Proposed Construction is Inconsistent with Mortality Studies in CHF Patients

The mortality studies outlined in the specification make clear that "mortality" was not merely a change in quality or condition of being mortal, but the difference between survival and death. The Office's construction of decreasing a risk of mortality as encompassing the symptomatic and hemodynamic effects attributed by Metra is improperly inconsistent with this guidance. *Bond* at 833; *Morris* at 1054.

During the mortality studies, mortality was monitored by a Data and Safety Monitoring Board (DSMB). The DSMB prematurely terminated the study "because of the favorable effect of [carvedilol] on survival... [that] represented a reduction in risk of death by [carvedilol] of 67%." ('821 patent, col. 6, ll. 56-62 (emphasis added).) It is further explained that this represented a "substantial (67%) reduction in the mortality of patients with chronic CHF." ('821 patent, col. 7, ll. 3-6.) The parallel between the two sentences, both referring to the same 67% reduction, evidences that a "reduction in risk of death" and "reduction in the mortality" are one in the same.

The Office's proposed construction of decreasing a risk of mortality by encompassing the hemodynamic and sympomatic effects attributed to Metra is inconsistent with the Applicant's use of "mortality" when describing the mortality studies in that it ignores the stated equivalence of "reduction in risk of death" and "reduction in the mortality." This still further evidences the impropriety of the Office's construction.

4. Conclusion with Respect to the Office's Construction of "Reducing The Risk of Mortality"

The "broadest reasonable interpretation" of the claims by the Office must be consistent with the specification. *Morris* at 1054. However, the Office has proposed constructions that are incompatible with the specification, contrary to the art cited

therein, and inconsistent with the Applicant's reported mortality studies. The Office's constructions are, therefore, improper.

Further, the Office has not presented any evidence that one skilled in the art would have understood the claims to encompass the mere treatment of hemodynamic and quality of life symptoms attributed to Metra. The Office citation to Stedman's (Office Action, pg. 6, 10), do justify a construction inconsistent with the specification and not overcome this deficiency.[2]

B. METRA FAILS TO TEACH OR SUGGEST THE CLAIMED METHOD OF TREATING TO DECREASE A RISK OF MORTALITY

For at least the reasons set forth in Applicant's April 2, 2007, Response, including the Affidavit of Dr. Lukas included therewith, Metra fails to teach or suggest a method of treating with carvedilol to decrease a risk of mortality. (April 2, 2007, Response, pg. 2-7 (incorporated herein).) Further, as shown above, the construction applied by the Office to allegedly encompass Metra is improper.

Importantly, the uncontroverted evidence is that, as Dr. Lukas stated, "[Metra] would not teach a practicing cardiologist anything about the use of carvedilol for the treatment of CHF or reduction of mortality in patients suffering from CHF." (April 2, 2007, Response, Exhibit 1, ¶89 (emphasis added).) As such, it cannot anticipate the rejected claim. *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985) ("The proper test of a publication as a § 102(b) bar is whether one skilled in the art to which the invention pertains could take the description of the invention in the printed publication and combine it with his own knowledge of the particular art and from this combination be put in possession of the invention on which a patent is sought."); *Eames v. Andrews*, 122 U.S. 40, 69 (1887) (affirming finding that reissue claims to a process for driving

underground water by use of a driven well were not anticipated by prior art printed publications where "[t]here is nothing in these extracts to suggest the peculiarities which distinguish the driven well as described in the reissued patent; and it may be said, in general, of all the extracts contained anything in actual and practical use, that, so far as they undertake to describe anything in actual and practical use, they point merely to the ordinary bored artesian well, or the instruments and implements to be used in its construction.")

Accordingly, Applicant respectfully requests that the Office reconsider and withdraw the rejection under 35 U.S.C. § 102(a).

IV. Rejection under 35 U.S.C. § 103(a)

Claims 1, 2, 7, 10, 11, 20, 21, 26, and 30 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Olsen (Olsen et al., Journal of the American College of Cardiology, Vol. 21, No. 2:141A, Abstract 725-2 (February 1993)) and Metra. (Office Action, pg. 5.) Further, claims 1-8 and 10-30 have been rejected under § 103(a) as being unpatentable over Olsen and Metra in view of The Merck Index and Schnurr (Schnurr et al., Journal of Cardiovascular Pharmacology, Vol. 10, Suppl. 11, S101-S107 (1987)). (Office Action, pg. 7.) Applicant respectfully disagrees with and traverses these rejections.

The rejections commonly rely upon the Office's characterization of Metra as disclosing a reduction in a risk of mortality in patients suffering from CHF. (*E.g,* Office Action, pg. 6, 8.) Applicant disagrees and asserts that the cited references do not teach or suggest a method of decreasing or reducing a risk of mortality. Furthermore, the Office has not addressed the evidence that the art taught away from the use of beta blockers for the treatment of mortality. The Office has also not addressed the evidence

of secondary considerations, including unexpected results, long-felt need, and surprise, all of which objectively support the non-obviousness of the claimed subject matter.

A. THE COMBINATION OF OLSEN AND METRA DOES NOT TEACH A REDUCTION IN MORTALITY IN CHF PATIENTS

For the reasons stated in Section III above and those of record, Metra fails to teach or suggest a method of treating with carvedilol to decrease or reduce a risk of mortality. (April 2, 2007, Response, pg. 2-7 (incorporated herein).) Olsen has not been cited for and does not overcome this deficiency. Because Olsen and Metra (individually or in combination) does not teach or suggest a method of treating with carvedilol to decrease a risk of mortality, the references do not render obvious the claimed subject matter.

B. THE MERCK INDEX WAS PUBLISHED AFTER THE FILING DATE AND IS NOT PRIOR ART

In addition to the aforementioned deficiencies, the Office's rejection based on Olsen and Metra in view of The Merck Index and Schnur is further defective. In particular, the Merck Index, published in 1999 according to the Office's citation on the PTO-892, is not prior art in view of the February 6, 1997, priority date for the present application. Further, the Merck Index appears to include the reporting of the inventor's own data, and as such, may not be prior art for this additional reason.

C. SCHNURR RELATES TO HYPERTENSION AND IS NOT INSTRUCTIVE REGARDING A DOSING SCHEDULE FOR CHF PATIENTS

The Office acknowledges that neither Olsen nor Metra teach "dosage administration during maintenance period beyond 4 months" as recited in claims 3-6, 8, 14, 15, 17, 18, 22, 23, and 25-29. (Office Action, pp. 8-9.) While Schnurr is cited to

overcome this deficiency, Schnurr relates to the treatment of hypertension, not CHF. As articulated by Dr. Wehling, doses and dosing schedules for CHF patients are quite different from those used in other indications, such as hypertension. (April 11, 2007 Reply to Office Action, Exhibit 3 at ¶11.) Moreover, one of ordinary skill would not have had a reasonable expectation of success based on the state of the art at the time of the invention. (*Id.*) Accordingly, there is no reason why one skilled in the art would have relied on the hypertension indication of Schnurr for treating mortality.

D. THE OFFICE HAS NOT ADDRESSED EVIDENCE OF TEACHING AWAY AND UNEXPECTED RESULTS

While Applicant maintains that a prima facie case of obviousness has not been established, evidence of teaching away and unexpected results contained in the specification and record is substantial and demonstrates objectively the non-obviousness of the claimed subject matter. For example, in addition to the results of a death rate reduction of 67% reported in the specification (*e.g.,* '821 patent, col. 6, ll. 40-col. 7, ll. 67), there is also evidence of unexpected results submitted with the April 2, 2007 Reply to Office Action (*e.g.*, April 2, 2007, Reply to Office Action, Exhibits 1, 3, and 4).

However, the Office has improperly failed to address this evidence on the record. MPEP 716.01(d). ("[E]ach piece of rebuttal evidence should not be evaluated for its ability to knockdown the prima facie case. All of the competent rebuttal evidence taken as a whole should be weighed against the evidence supporting the prima facie case. *In re Piasecki*, 745 F.2d 1468, 1472, 223 USPQ 785, 788 (Fed. Cir. 1984)."). Further, the Office has not identified <u>any</u> reasons why this unrebutted evidence is not persuasive. MPEP § 716.01(d) ("If, after evaluating the evidence, the examiner is still not convinced

that the claimed invention is patentable, the next Office action should include a statement to that effect and identify the reason(s) (e.g., evidence of commercial success not convincing, the commercial success not related to the technology, etc.); MPEP § 2144.08, paragraph II.B ("[O]nce the applicant has presented rebuttal evidence, Office personnel should reconsider any initial obviousness determination in view of the entire record. *See, e.g., Piasecki*, 745 F.2d at 1472, 223 USPQ at 788; *Eli Lilly*, 902 F.2d [943,] 945, 14 USPQ2d [1741,] 1743 [(Fed. Cir. 1990)]. All the proposed rejections and their bases should be reviewed to confirm their correctness. Only then should any rejection be imposed in an Office action. The Office action should clearly communicate the Office's findings and conclusions, articulating how the conclusions are supported by the findings.").)

Further, Applicant also expressly traverses the Office's contention, as applied to the present facts, that "it is not inventive to discover the optimum or workable ranges by routine experimentation." (Office Action, pg. 9 (citing *In re Aller*, 220 F.2d 454 (C.C.P.A. 1955)).) Among other things, as the court acknowledged in *Aller*, "under some circumstances, changes such as these may impart patentability to a process if the particular ranges claimed produce a new and unexpected result." *Id.* at 456 (emphasis added).

1. The Invention was Contrary to the Teachings of the Art

As addressed in the April 2, 2007 Reply to Office Action, the prevailing dogma throughout the 1980's and until about 1997 was that beta-blockers were contraindicated for the treatment of CHF patients. (April 2, 2007, Reply to Office Action, Exhibit 1 at ¶¶28, 44-45.) Beta blockers were contraindicated in patients suffering from CHF because they were known to have undesirable cardiodepressive effects. (April 2, 2007

Reply to Office Action, Exhibit 3 at ¶¶7-9; Exhibit 1 at ¶¶ 44-45.) This view was supported by early clinical results where patients with angina and CHF worsened or did not improve with beta-blockers. (April 2, 2007, Reply to Office Action, Exhibit 1 at ¶¶28, 44-45, 55 (beta-blocker xamoterol was shown to worsen survival in patients with severe heart failure), 56 (beta-blocker metropolol was shown to improve exercise tolerance and cardiac function, but had no beneficial effect on mortality), 57 (no statistically significant decrease in mortality with beta-blocker bisoprolol).) Indeed, the clinical testing of beta blockers had failed to show any significant decrease in mortality in CHF patients prior to the present invention. (April 2, 2007 Reply to Office Action, Exhibit 3.) Thus, the use of carvedilol (a beta blocker) to treat mortality would have been counter to the expectations and experience of one skilled in the art, and would not have been obvious.

Dr. Lukas explains that "[t]his contradiction was due to the fact that the compensatory activation of the sympathetic nervous system a patient with heart failure, which is the short term attempt by the body to support the failing circulation by increasing blood pressure and heart rate, was thought to be so essential that blocking it could result is significant clinical deterioration or even death for the patient with heart failure." (April 2, 2007 Reply to Office Action, Exhibit 1 at ¶ 45.) Thus, the very cardiodepresseive effects of heart rate and pressure reduction attributed by the Office to Metra (*e.g.*, Office Action, pg. 5) would have directed one away form using carvedilol to reduce or decrease a risk of mortality because such effects "could result is significant clinical deterioration or even death for the patient with heart failure." (*Id.*)

2. The Invention was not Predictable from the Art

With regard to symptomatic treatment, Dr. Lukas explained that "[c]linincal research has demonstrated that symptomatic improvement does not predict the effect of

the treatment on mortality." (April 2, 2007, Reply to Office Action, Exhibit 1 at ¶52, *see also* ¶¶46-51, 53-58.) At least due to the recognized distinction between symptomatic treatment and treatment to decrease mortality risk, Applicant respectfully submits that one skilled in the art would not have understood, or been motivated, by any disclosure in Metra regarding carvedilol or symptomatic treatment using the same to be a teaching of or a suggestion for using carvedilol for decreasing a risk of mortality. Indeed, as Dr. Lukas attested, "[Metra] would not teach a practicing cardiologist anything about the use of carvedilol for the treatment of CHF or reduction of mortality in patients suffering from CHF." (April 2, 2007 Reply to Office Action, Exhibit 1, ¶89 (emphasis added).)

3. The Mortality Reduction was Particularly Unexpected and Fulfilled a Long-Felt Need

In the first clinical study (the "GSK carvedilol study") to examine carvedilol's effects on mortality, a dramatic mortality reduction of about 67% was found for all cases in class II-IV CHF patients. (*E.g.*, '821 patent, col. 6, ll. 43 - col. 7, ll. 67.) A later larger-scale study (the "COPERNICUS Study") focusing on CHF patients with severe heart failure confirmed the surprising ability of carvedilol to reduce mortality in CHF patients, finding a 35% mortality reduction in these severe-heart failure patients. The published results of the COPERNICUS Study explain that "if physicians treated 1000 patients with severe heart failure similar to that in [the COPERNICUS study] with carvedilol for one year, approximately 70 premature deaths would be prevented." M. Packer *et al.* "Effect of Carvedilol on Survival in Severe Chronic Heart Failure," 344(22) New England J. Med., 1651-1658, 1657 (May 31, 2001) (Reference no. 99 of Applicant's December 28, 2004, IDS).) The COPERNICUS Study results are compared to the only prior large-scale study of using a beta-blocker (bucindolol) in patients with

severe heart failure, which suggested that beta-blockers may adversely affect patients at the highest risk. (*Id.* at pg. 1651.)

As evidenced by Dr. Wehling's Declaration, it would have been unexpected for carvedilol to reduce mortality in CHF patients; therefore, the mortality reduction in initial testing of about 67% was particularly unexpected, fulfilling a long-felt need. (April 2, 2007 Reply to Office Action, Exhibit 3 at ¶¶7, 10, 14, 18; Exhibit 1 at ¶¶64, 65, 70.)

4. The Results Were Considered Surprising

The surprising results of the GSK Carvedilol Study caused the study to be prematurely terminated so that the placebo group could be offered carvedilol. (*E.g.*, '821 patent, col. 6, ll. 54-59.) The surprising nature of these results was reported at that time, including in the February 20, 1995 edition of *Chemistry and Industry* (London), No. 4, page 123 contained an article titled "SmithKline Beecham: unexpected success halts drug trial." (Reference no. 41 of Applicant's December 28, 2004, IDS.) As reported in this article, "An independent monitoring group has told [GSK] to halt US trials of [carvedilol] because it's more effective than expected." (*Id.*) The article quotes the DSMB as having stated "to continue administering placebo would be unethical in view of . . . preliminary reviews of the mortality data." (*Id.*)

The published results of the GSK Carvedilol Study further evidence the significant and unexpected mortality reduction that caused the DSMB to prematurely halt the study. (M. Packer *et al.*, "The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group," New England J Med. 334(21): 1349-55 (May 23, 1996), reference no. 70 of Applicant's December 28, 2004, IDS.) As reported by Packer, "[r]andomization [of patients for the study] began on April 29, 1993, and the study was stopped early on the

recommendation of the [DSMB] on February 3, 1995. This decision was based on the finding of a significant effect of carvedilol on survival — an effect that exceeded all conventional boundaries used to stop clinical trials." (*Id.* at pg. 1350 (citations omitted).) As reported by Packer, the mortality reduction for patients having mild to severe CHF was 65%. (*Id.* at pg. 1350.)

E. CONCLUSION WITH RESPECT TO NON-OBVIOUSNESS

For the reasons above and those of record, Applicant requests the reconsideration and withdrawal of the rejections under 35 U.S.C. § 103.

V. Conclusion

In view of the foregoing remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims. The Examiner is invited to contact Applicant's undersigned representative by telephone at (202) 408-4092 to discuss this case.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: August 13, 2007

By: _____
Mark J. Feldstein
Reg. No. 46,693

Attachments:

A - Stedman's Medical Dictionary, 26th Ed. (1995), pg 1054
B - Applefeld, M.M., (1986) Am. J. Med., 80, Suppl. 2B, 73-77
C - Waagstein, The Lancet, 342 (1993), 1441-1446
D - The Cardiac Insufficiency Bisoprolol Study (CIBIS), Circulation, 90, No. 4 (1994), 1765-1773

ATTACHMENT A

STEDMAN'S
Medical Dictionary

26th Edition

ILLUSTRATED IN COLOR

Williams & Wilkins
Baltimore • Philadelphia • Hong Kong
London • Munich • Sydney • Tokyo
A WAVERLY COMPANY

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Database design by Lexi-Comp Inc., Hudson, OH
Printed in the United States of America by R.R. Donnelley & Sons Company

English Language Co-editions
Asian 1967, 1972, 1976
Indian 1967, 1973
Taiwan 1972, 1978

Translated Editions
Greek 1976
Indian 1977
Japanese 1977, 1985, 1995
Portuguese 1976, 1995
Spanish 1993

Library of Congress Cataloging-in-Publication Data

Stedman, Thomas Lathrop, 1853-1938.
[Medical dictionary]
Stedman's medical dictionary.—26th ed.
p. cm.
ISBN 0-683-07922-0 REGULAR EDITION
ISBN 0-683-07935-2 DELUXE EDITION
1. Medicine—Dictionaries. I. Title. II. Title: Medical dictionary.
[DNLM: 1. Dictionaries, Medical. W 13 S812m 1995]
R121.58 1995
610'.3—dc20
DNLM/DLC
for Library of Congress

bar or horseshoe-shaped piece of iron or steel that has been made magnetic by contact with another m. or, as in an electromagnet, by passage of electric current around a metallic (iron) core. **3.** An electromagnet built in a cynlindrical configuration to accommodate a patient in its core, for magnetic resonance imaging. [G. *magnēs*]

superconducting m., a m. whose coils are cooled, usually with liquid helium, to a temperature at which the metal becomes superconducting, effectively removing all electrical resistance.

mag·net·ic. **1.** Relating to or characteristic of a magnet. **2.** Possessing magnetism.

mag·ne·tism (mag′nĕ-tizm). The property of mutual attraction or repulsion possessed by magnets.

animal m., a psychic force akin to the property of mutual attraction or repulsion possessed by metal magnets and once believed to be the principal factor in hypnosis, which thus was called animal m. SEE hypnosis, mesmerism.

mag·ne·to·car·di·og·ra·phy (mag′nĕ-tō-kar-dē-og′ră-fē). Measurement of the magnetic field of the heart, produced by the same ionic currents that generate the electrocardiogram, and showing characteristic P, QRS, T, and U waves.

mag·ne·to·en·ceph·a·lo·gram (MEG) (mag-nē′tō-en-sef′ă-lō-gram). A gauss-time record of the magnetic field of the brain.

mag·ne·to·en·ceph·a·log·ra·phy (mag-nē′tō-en-sef-ă-log′ră-fē). The process of recording the brain's magnetic field.

mag·ne·tom·e·ter (mag-nĕ-tom′ĕ-ter). An instrument for detecting and measuring the magnetic field.

mag·ne·ton (mag′nĕ-ton). A unit of measurement of the magnetic moment of a particle (*e.g.*, atom or subatomic particle).

Bohr m., a constant in the equation relating the difference in energies between parallel and antiparallel spin alignments of electrons in a magnetic field; the net magnetic moment of one unpaired electron; used in electron spin resonance spectrometry for detection and estimation of free radicals. SYN electron m.

electron m., SYN Bohr m.

nuclear m., a constant in the equation relating the difference in energies between parallel and antiparallel spin alignments of atomic nuclei in a magnetic field; used in nuclear magnetic resonance spectrometry.

mag·ne·to·ther·a·py (mag-nē′tō-thār′ă-pē). Attempted treatment of disease by application of magnets.

mag·ni·fi·ca·tion (mag′ni-fi-kā′shŭn). **1.** The seeming increase in size of an object viewed under the microscope; when noted, this increased size is expressed by a figure preceded by ×, indicating the number of times its diameter is enlarged. **2.** The increased amplitude of a tracing, as of a muscular contraction, caused by the use of a lever with a long writing arm, *i.e.*, one in which the fulcrum is placed nearer to the muscle than to the writing point. [L. *magnifico*, pp. *-atus*, to magnify]

mag·ni·tude (mag′ni-tūd). Size or extent.

average pulse m., the amplitude of pulse averaged throughout its duration; identical with peak amplitude for a square wave or pulse without droop.

peak m., the greatest amplitude.

mag·no·cel·lu·lar (mag′nō-sel′yū-lăr). Composed of cells of large size. [L. *magnus*, large, + cellular]

mag·num (mag′nŭm). SYN capitate (1). [L. *magnus*, large]

Magnus, Rudolph, German physiologist, 1873–1927. SEE M.'s *sign*.

mag·nus (mag′nŭs). Large; great; denoting a structure of large size. [L.]

Mahaim, I. SEE M. *fibers*, under *fiber*.

Ma-huang (mah-hwahng). Name for *Ephedra equisetina*. [Chinese]

MAI. Abbreviation for *Mycobacterium avium-intracellulare*. SEE ALSO *Mycobacterium avium-intracellulare complex*.

maid·en·head (mā′den-hed). Obsolete term for the intact hymen of a virgin.

mai·dism (mā′dizm). SYN pellagra. [*Zea mays*, maize]

Maier, Rudolf, German physician, 1824–1888. SEE M.'s *sinus*.

maim (mām). To disable or cripple by an injury.

main (man). SYN hand. [Fr.]

m. d'accoucheur, SYN accoucheur's *hand*.

m. en crochet, a permanent flexure of the fourth and fifth fingers, resembling the hand of a woman crocheting with three fingers bent to guide the thread.

m. en griffe, SYN clawhand.

m. en lorgnette, SYN opera-glass *hand*.

m. fourchée, SYN cleft *hand*.

m. succulente, SYN Marinesco's succulent *hand*.

main·frame (mān′frām). A large digital computer, such as would be used in a hospital for information management. Cf. mini.

main·stream·ing (mān′strēm-ing). Providing the least restrictive environment (socially, physically, and educationally) for chronically disabled individuals by introducing them into the natural environment rather than segregating them into homogeneous groups living in sheltered environments under constant supervision.

main·tain·er (mān-tā′ner). A device utilized to hold or keep teeth in a given position.

space m., an orthodontic appliance used to prevent the loss of space or the shifting of teeth following extraction or premature loss of teeth. SYN space retainer.

main·te·nance (mān′ten-ans). **1.** A therapeutic regimen intended to preserve benefit. Cf. compliance (2), adherence (2). **2.** The extent to which the patient continues good heath practices without supervision, incorporating them into a general life-style. Cf. compliance. [M.E., fr O.Fr., fr. Mediev. L. *manuteneo*, to hold in the hand]

maise oil (māz). SYN corn oil.

Maissiat, Jacques H., French anatomist, 1805–1878. SEE M.'s *band*.

Majocchi, Domenico, Italian dermatologist, 1849–1929. SEE M. *granulomas*, under *granuloma*; M.'s *disease*.

ma·jor (mā′jŏr). Larger or greater in size of two similar structures. [L. comparative of *magnus*, great]

Makeham, William Matthew, English actuary, †1892. SEE M.'s *hypothesis*.

mal (mahl). A disease or disorder. [Fr. fr. L. *malum*, an evil]

m. de caderas, a disease of horses in some South American countries caused by the protozoan parasite *Trypanosoma equinum* and manifested by emaciation, remittent fever, weakness (especially of the hindquarters, from which the disease gets its name), and eventually death; the trypanosome has a reservoir in the giant rodent, the capybara; cattle, sheep, and goats are only mildly affected; humans are not susceptible.

m. de Cayenne, SYN elephantiasis.

m. de la rosa, m. rosso, SYN pellagra.

m. de los pintos, SYN pinta.

m. de Meleda, endemic symmetrical keratoderma of the extremities occurring on the island of Meleda off the coast of Dalmatia.

m. de mer, SYN seasickness.

m. de San Lazaro, SYN elephantiasis.

grand m. (grahn), SYN generalized tonic-clonic *seizure*.

m. perforant, SYN perforating *ulcer* of foot.

petit m. (pĕ-tē′), type of seizure. [Fr. small]

mal-. Ill, bad; opposite of eu-. Cf. dys-, caco-. [L. *malus*, bad]

ma·la (mā′lă). **1.** SYN cheek. **2.** SYN zygomatic *bone*. [L. cheek bone]

mal·ab·sorp·tion (mal-ab-sōrp′shŭn). Imperfect, inadequate, or otherwise disordered gastrointestinal absorption.

congenital selective glucose and galactose m., an inherited disorder in which D-glucose and D-galactose accumulate in the intestinal lumen and exert an osmotic effect; leads to abdominal fullness, abdominal pain, and diarrhea.

enterocyte cobalamin m., an inherited disorder of impaired transintestinal transport of cobalamin; symptoms are similar to a vitamin B_{12} deficiency.

fructose m., an inborn error in metabolism in which oral D-fructose is incompletely absorbed; results in abdominal symptoms and diarrhea.

ATTACHMENT B

Chronic Congestive Heart Failure

Where Have We Been? Where Are We Heading?

MARK M. APPLEFELD, M.D.
Baltimore, Maryland

Chronic congestive heart failure is a frequently occurring disease associated with an impaired quality of life and significant mortality rate. Progress has been made in dissecting the pathophysiologic changes of congestive failure and in using vasodilators, newer positive inotropic agents, and other treatment modalities. Despite these advances, the overall mortality rate from congestive heart failure has not decreased. Further, many unanswered questions remain: How and why does a myocardial cell die? How should quality of life be measured? When should vasodilators and positive inotropic agents be given? What role do receptors play in pathogenesis and therapy? Can sudden death in heart failure be prevented? These and other questions will provide the stimulus for further studies in congestive heart failure.

In 1983, Braunwald [1] reported that congestive heart failure affected four million patients in America. In this symposium, Franciosa [2] indicated that the prevalence of congestive failure may be somewhat lower (i.e., two to three million patients), with an annual incidence of approximately 250,000 cases. In addition to being a frequently occurring disease, congestive heart failure is an economic burden in terms of the health care dollars expended annually. For example, if one of every five patients with congestive failure (i.e., 20 percent) requires one hospital admission per year for the disease at a cost for this hospitalization of $3,000 [3], there is a yearly expenditure of $1.8 billion to $2.4 billion for congestive failure inpatient care alone. If medication costs and physician services (both inpatient and outpatient) are added to this figure, an even greater portion of the health care dollar is consumed by congestive heart failure.

How serious is the prognosis for patients who have congestive failure? More than a decade ago, data from the Framingham study [4] demonstrated a 24-month mortality rate of 31 percent and a 48-month mortality rate of 52 percent among patients with congestive failure. Despite the addition of vasodilators for treatment of congestive failure during the past decade, this serious prognosis has not changed appreciably. For example, Franciosa et al [5] reported 12- and 36-month mortality rates of 25 percent and 65 percent, respectively, in patients with congestive failure caused by either coronary heart disease or idiopathic dilated cardiomyopathy. To cast these mortality rates in a different perspective, the survival data in **Figure 1** are derived from patients with squamous cell carcinoma of the lung [6]. As can be observed, in patients with stage III disease (i.e., metastatic), survival at 12 and 36 months following a diagnosis of metastatic squamous cell cancer approximates that of patients with congestive failure. Thus, the analogy can be reached that congestive failure is the

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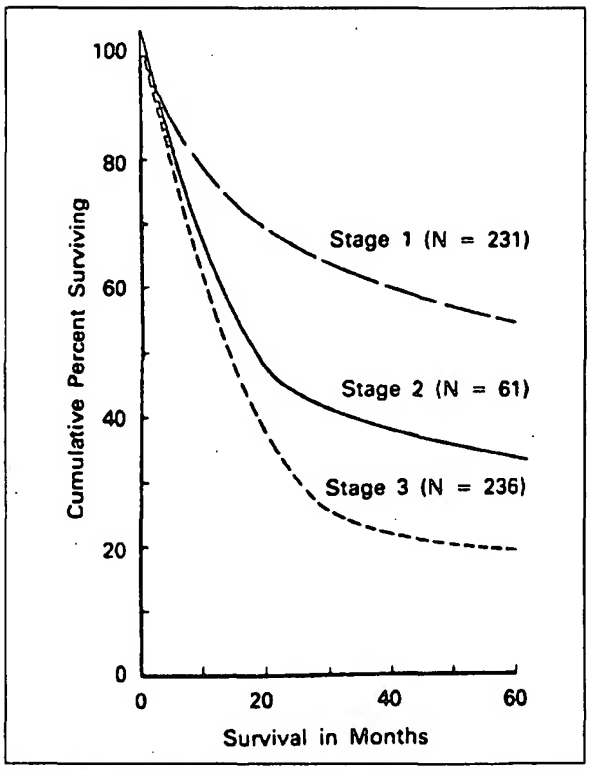

Figure 1. *Survival of patients with squamous cell carcinoma of the lung after surgical treatment, by pathologic stage. (Reproduced with permission from [6].)*

cancer of the heart. However, unlike some forms of cancer (e.g., Hodgkin's disease, non-Hodgkin's lymphoma, oat cell carcinoma of the lung, and acute myelogenous leukemia) in which newer therapeutic approaches have resulted in improved survival rates over the past two decades, similar advances—except for cardiac transplantation—have not been realized in congestive heart failure.

In congestive heart failure, myocardial damage causes myocardial failure (**Figure 2**), which in turn causes a reduction in cardiac output and elevation in left ventricular end-diastolic pressure. As a consequence, compensatory mechanisms (i.e., the autonomic nervous system and renin-angiotensin system) are activated to increase circulating blood volume and maintain perfusion to vital organs (the kidneys and brain). These compensatory mechanisms increase preload and afterload, increase ventricular end-diastolic volume and wall tension, and raise myocardial oxygen demands. A vicious cycle is thus established in which the myocardium becomes increasingly disadvantaged and in which "congestive heart failure begets further congestive heart failure." As heart failure becomes progressively more advanced, the ability to intervene beneficially becomes progressively limited. As noted earlier in this symposium issue [7], our understanding of why and how a myocardial cell dies and becomes replaced by fibrous tissue is rudimentary at best. This very basic problem merits active investigation.

Unverferth and Baker [8] noted that endomyocardial biopsy can be performed by physicians adept in the technique with acceptably low complication rates (i.e., less than 0.5 percent). Currently, endomyocardial biopsy is a useful tool to determine the severity of myocardial histologic changes in cancer patients who receive anthracycline antibiotics, to assess the presence and severity of rejection after cardiac transplantation, and to confirm a suspected clinical diagnosis of myocarditis. However, the histologic interpretation of these samples is still imperfect. Thus, the definition of what constitutes a significant inflammatory response is still debated. Further, as with any technique in which a small tissue sample is obtained, there are uncertainties as to the relevance of such biopsy changes to morphologic changes in the whole organ. Finally, it is not known whether the use of immunosuppressive drugs in patients with myocarditis and cellular infiltrates will retard, stabilize, or even potentially accelerate the ultimate development of myocardial fibrosis. If it can be shown that patients with chronic heart failure frequently have inflammatory cells on endomyocardial biopsy and that these infiltrates can be eradicated and the development of myocardial fibrosis can be prevented by immunosuppressive therapy, then this technology may become very important in the management of these patients. An exciting observation made by Unverferth and Baker [8] is that at least some forms of cardiomyopathy are caused by inherited biochemical defects. This concept takes us one step closer to an understanding of the pathophysiologic events of a disease—cardiomyopathy—frequently results in chronic congestive failure.

What therapeutic goals should guide the management of congestive failure [7]? The initial aim should be hemodynamic improvement, to increase cardiac output, reduce left ventricular filling pressure and right atrial pressure, and thus improve overall function of the heart as well as other organ systems—the kidneys, liver, and brain. The long-term goals would be to maintain improved cardiac function and reverse the abnormal pathophysiologic events just discussed. Additionally, both the quality of life and the longevity of these patients should be improved. Given the drugs currently available to treat congestive failure, these last two goals may be mutually exclusive. Although the quality of life in these patients may be improved, it is apparent that—except through cardiac transplantation—their survival [4,5,9] has not been increased. In treating congestive heart failure, it is important that basic therapeutic principles not be overlooked. Adequate rest, restricted salt and fluid intake, control of other complicating medical problems (hypertension, anemia, hypoxemia, or hyperthyroidism) and adequate doses of digitalis and diuretics should be emphasized.

"Whenever one is asked to speculate on the future, one

invariably discusses the past" [10]. During this symposium, attention has been focused upon the past because it is the gold standard against which our present therapy is measured. In 1937, Levine [11] noted that "digitalis is the most important drug in the treatment of congestive heart failure. Apart from digitalis or its allied drugs, there is little else in the form of medication that acts directly on the heart which one can use in the treatment of congestive heart failure." However, it is apparent that digitalis is an imperfect solution to the problem of congestive failure. The limitations of digitalis are highlighted by the high incidence of toxicity [12] (i.e., 25 to 30 percent of patients) and its decreasing positive inotropic effect as the severity of congestive failure advances. Further, it is clear that digitalis can safely be discontinued in some patients with heart failure. Except by clinical trial and clinical error, we do not yet know how to identify such patients, although it appears that the presence of normal sinus rhythm and the absence of a third heart sound may be predictive of successful digoxin withdrawal.

The alternative positive inotropic agents currently available for clinical use are dobutamine, dopamine, and amrinone. These drugs must be administered intravenously, and the pharmacologic and clinical differences between them are not as striking as commonly believed [13]. Each of these drugs may be administered on a long-term basis through portable infusion pumps. However, the use of such devices for this purpose has not yet been widely applied [14]. An alternative—albeit not necessarily cost-effective—to the use of such devices would be repeated, frequent hospitalizations for administration of these drugs. Unfortunately, the search for the ideal drug to replace digitalis will not be completed in 1985.

The practice of medicine is being increasingly constrained by outside forces, and the expenditure of health care dollars is being closely scrutinized. There are costs assigned to admitting patients to a coronary care unit, inserting a thermodilution catheter and performing complicated (and sometimes confusing) hemodynamic drug trials [15], radionuclide angiocardiography, continuous electrocardiographic recording, echocardiography, and exercise testing. There are no clear guidelines for the use of these tests in the management of congestive heart failure. For example, how frequently should exercise testing be performed to quantitate an improvement in functional capacity after a new drug has been started? How often should continuous electrocardiographic recording be used to determine whether there has been a significant change in the frequency of ventricular ectopy from an antiarrhythmic agent? Do antiarrhythmic drugs change the incidence of sudden death in patients with congestive failure [16]? How should improvement in the quality of life be measured in these patients? These and other important issues have not been addressed in this symposium.

A question that may be of greater theoretic than practical concern is whether or not the failing myocardium should be stimulated by positive inotropic agents [17]. Indeed, it has not yet been conclusively demonstrated that stimulating the failing myocardium is more deleterious than doing nothing in patients with advanced congestive heart failure and severely compromised quality of life. The inexplicable disease progression inherent in congestive heart failure clouds resolution of this issue.

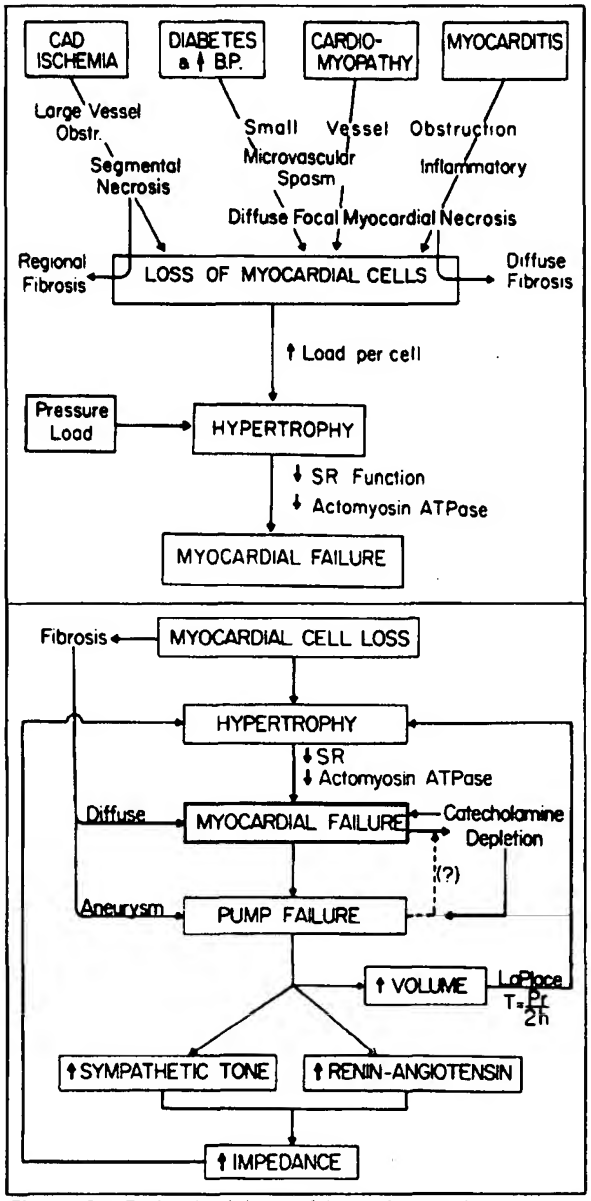

Figure 2. *Pathophysiology of heart failure. (Reproduced with permission from [1].)*

In this symposium, Sutton [18] reviewed the use of vasodilators in congestive failure. These drugs act by reducing either preload or afterload or both and thus permit more efficient myocardial function. Approximately 35 to 45

percent of patients note symptomatic improvement with hydralazine or prazosin, and captopril is associated with significantly greater efficacy (i.e., 60 to 70 percent). However, despite the improvement in functional capacity with the use of these drugs, they do not improve survival rates in congestive failure [19]. Additionally, long-term administration of these drugs is sometimes associated with adverse effects that limit their use.

Baughman [20] reviewed the use of the calcium channel antagonists in congestive heart failure. He noted that all of these drugs currently available have negative inotropic effects that are usually counterbalanced by their potent vasodilatory effects. Since clinical experience with these drugs in congestive failure is still limited, an assessment cannot be made of their proper role.

Can a reasonable approach to drug therapy in congestive heart failure be suggested? In my view, the answer to this question is "yes." Digitalis and diuretics remain an appropriate initial combination in treating symptomatic heart failure. If congestive symptoms persist after use of these drugs and the systolic blood pressure is greater than 100 or 110 mm Hg, a vasodilator should be added. Captopril is a good choice and is specifically approved by the FDA for this use. Although initially considered to be only adjunctive drugs, nitrates should be used earlier in this disease, since they reduce right ventricular preload and thus improve right ventricular function [2]. If the systolic blood pressure is between 90 and 100 mm Hg, captopril and nitrates should be prescribed at reduced dosages so that hypotension may be avoided. Changes in the dosages of these drugs may be made weekly, but only after a careful history and physical examination. If the systolic blood pressure initially is less than 90 mm Hg, serial testing of hemodynamic efficacy using several different drugs and thermodilution catheters is preferable. The absence of a salutary clinical and/or hemodynamic response during such invasive testing makes the selection of an appropriate drug difficult. Moreover, a beneficial hemodynamic effect during short-term drug testing does not necessarily connote long-term efficacy.

Fisher and Ruffolo and their co-workers [21,22] shared their observations of the importance of receptors in congestive failure. In the discussion of Fisher et al [21], the important question is asked of whether some patients with congestive failure should be treated with beta receptor blockade. Clearly, there have been dramatic successes with the use of beta blockers in congestive failure. Unfortunately, it is currently impossible to correctly identify these patients without actually giving them a drug that may be potentially harmful. Ruffolo and Kopia [22] indicated that there is a reduction in both the number of beta receptors and the production of cyclic AMP by these receptors in congestive failure. There are no spare beta-adrenegic receptors within the myocardium. This fact may be important in the pathophysiology of congestive failure. Whether or not alpha-adrenergic myocardial receptors are clinically important is uncertain. It is conceivable that specific receptor assays will be routinely requested in the future to assist in the selection of drug therapy for these patients.

The New York Heart Association functional classification for patients with congestive failure is still commonly used. Reports in this symposium appear to indicate that patients with New York Heart Association functional class III or IV disease are divided into nonhomogeneous subgroups. These subgroups are important because they determine the response to selected therapy—some patients show response to vasodilators, some to positive inotropic drugs; some to calcium channel antagonists, and some to combinations of these three drug classes. Perhaps, as we begin to dissect congestive heart failure further, patients with New York Heart Association class I or II disease will also be found to be divided into similar subsets, for which therapy may also need to be individually selected.

Finally, what does the future hold for congestive heart failure? With the availability of improved organ procurement techniques and newer anti-rejection drugs, cardiac transplantation has already assumed increasing importance [23]. We are currently in an exciting era of clinical and laboratory investigation in congestive failure. We now have new drugs and new modalities of therapy. We are also discovering new concepts about older drugs and older modalities of therapy. A cure for congestive heart failure may never be found. However, inroads have been made into an understanding of the basic pathophysiologic mechanisms and therapy of this disease. With this impetus, there is every reason to be optimistic about our abilities to treat this disease in the future.

ACKNOWLEDGMENT

I wish to thank Mrs. Kate McWilliams for her assistance in the preparation of this manuscript.

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ATTACHMENT C

THE LANCET

Articles

Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy

Finn Waagstein, Michael R Bristow, Karl Swedberg, Fulvio Camerini, Michael B Fowler, Marc A Silver, Edward M Gilbert, Maryl R Johnson, Franz G Goss, Åke Hjalmarson, for the Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group

Summary

Several small studies have suggested beneficial effects of long-term β-blocker treatment in idiopathic dilated cardiomyopathy. Our large multicentre study aimed to find out whether metoprolol improves overall survival and morbidity in this disorder.

383 subjects with heart failure from idiopathic dilated cardiomyopathy (ejection fraction <0·40) were randomly assigned placebo or metoprolol. 94% were in New York Heart Association functional classes II and III, and 80% were receiving background treatment. A test dose of metoprolol (5 mg twice daily) was given for 2–7 days; those tolerating this dose (96%) entered randomisation. Study medication was increased slowly from 10 mg to 100–150 mg daily. There were 34% (95% CI −6 to 62%, p=0·058) fewer primary endpoints in the metoprolol than the placebo group; 2 and 10 patients, respectively, deteriorated to the point of needing transplantation and 23 and 19 died. The change in ejection fraction from baseline to 12 months was significantly greater with metoprolol than with placebo (0·13 vs 0·06, p<0·0001). Pulmonary capillary wedge pressure decreased more from baseline to 12 months with metoprolol than with placebo (5 vs 2 mm Hg, p=0·06). Exercise time at 12 months was significantly greater (p=0·046) in metoprolol-treated than in placebo-treated patients.

In patients with idiopathic dilated cardiomyopathy, treatment with metoprolol prevented clinical deterioration, improved symptoms and cardiac function, and was well tolerated.

Lancet 1993; 342: 1441–46

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Introduction

It was first reported in 1975 that patients with congestive heart failure due to idiopathic dilated cardiomyopathy and with resting tachycardia improved greatly with long-term β-blockade.[1] Although this and confirmatory studies[2] were uncontrolled, a cause and effect relation between β-blockers and the improvement was strongly suggested by the observed deterioration when the drugs were withdrawn.[3] Improvement in survival was also suggested in a comparison of patients treated with β-blockers and matched historical controls.[4]

Since β-blocking agents could aggravate heart failure, β-blocker therapy was initially criticised. Scepticism about its efficacy was reinforced when two small, short-term (1-month) controlled trials failed to show any benefit, although the treatment was well tolerated.[5,6]

In the 1980s, experimental findings led to a resurgence of interest in the clinical use of β-blockade as treatment for heart failure.[7] Experiments in explanted failing human hearts provided evidence in the form of receptor desensitisation that failing human ventricles are subjected for a long time to high adrenergic activity.[8] Transmyocardial measurements of noradrenaline provided further support for the conclusion that the failing human heart is exposed long term to increased, not decreased, adrenergic activity. Previous studies in animal models of heart failure had reported cardiac noradrenaline depletion and supersensitivity to β-agonists.[10]

These data provided a basis for the idea that chronic adrenergic activation has a deleterious effect on the natural course of heart muscle disease.[7,11] Several small uncontrolled or placebo-controlled studies were done at the same time as we were planning and setting up our trial. All showed beneficial effects on cardiac function and symptoms[11–18] and some also reported favourable effects on exercise tolerance.[12,14,16,17] However, the question of whether overall survival and morbidity in idiopathic dilated cardiomyopathy can be improved by long-term β-blockade can be answered only by a large-scale multicentre trial, which we now report.

Subjects and methods

The Metoprolol in Dilated Cardiomyopathy (MDC) trial was a randomised, placebo controlled parallel-group trial of metoprolol on mortality and need for heart transplantation in patients with symptomatic idiopathic dilated cardiomyopathy. The study was carried out in 33 centres in Europe and North America. The protocol was approved by the institutional review board at each centre and all patients gave informed written consent. Data were collected and analysed at the coordinating centre (Sahlgren's Hospital, University of Göteborg, Sweden).

The primary objective was to study the effect of metoprolol on a combined fatal and non-fatal endpoint. The fatal component of the primary endpoint was all-cause mortality and the non-fatal component was clinical deterioration to a point at which cardiac transplantation would normally be offered as a treatment option. We assumed that the young patients with idiopathic dilated cardiomyopathy would be referred for heart transplantation if they deteriorated greatly. Need for heart transplantation was defined in the protocol as progression of heart failure symptoms combined with at least one of the following: a decrease in ejection fraction by 10 units or more; an increase in mean right atrial pressure (≥5 mm Hg) or mean pulmonary wedge pressure (≥10 mm Hg), or both, plus a fall in cardiac index (≥30%); and continuous or repeated need to be in hospital for heart failure. The need for a continuous hospital stay was defined as the inability to be discharged because of the severity of heart failure, difficulties with arrhythmias related to heart failure, or both, with or without temporary or permanent inotropic support. Repeated need for hospital admission was defined as three or more admissions for heart failure, arrhythmia, or both, during the 3 months before a decision was made to withdraw the patient from study medication. If patients were not eligible for transplantation because of a contraindication or because they did not have appropriate medical insurance, they could still meet the non-fatal endpoint criteria based on the medical need. All endpoints were reviewed by an endpoint committee (the executive group) unaware of group assignment, who rendered a final classification before the code was broken. Patients who did not satisfy our criteria but who were listed for transplantation were not considered to have reached a primary endpoint and were classified as study withdrawals. The first primary endpoint reached was used for classification.

The secondary objectives were to assess the effects of metoprolol on cardiac function, exercise capacity, quality of life, and hospital admission or emergency visits for heart failure treatment. With the exception of quality of life, New York Heart Association (NYHA) classification, and data on hospital stays and visits, data were available only in the subset of patients randomised before Jan 1, 1990. A simplified protocol was then adopted that included only clinical data. Only a few centres continued to use the original follow-up protocol after that date.

Eligible patients had symptomatic dilated cardiomyopathy and ejection fraction below 0·40 and were aged 16–75 years. Reasons for exclusion were treatment with β-blockers, calcium-channel blockers, inotropic agents (except digitalis), or high doses of tricyclic antidepressant drugs, significant coronary artery disease shown by angiography (>50% obstruction of a major epicardial vessel), clinical or histological signs of ongoing myocarditis, other life-threatening diseases, obstructive lung disease requiring β_2-agonists, excessive alcohol consumption (>700 g per week), drug abuse, insulin-dependent diabetes, phaeochromocytoma and thyroid disease. In addition, we required that patients had achieved a state of compensated heart failure by means of conventional heart failure treatment, which could include digitalis, diuretics, angiotensin-converting-enzyme (ACE) inhibitors, and nitrates. Systolic blood pressure had to be 90 mm Hg or more and heart rate 45 beats per min (bpm) or more. 417 patients satisfied all criteria and were given test doses of metoprolol (tartrate) 5 mg twice daily for at least 2 days and not more than 7 days. Patients who deteriorated after the test dose did not proceed to randomisation. Deterioration was defined as one or more of coughing in the supine position, basal pulmonary rales, increased symptoms of dyspnoea at rest, increased tricuspid regurgitation (increased jugular systolic venous pressure, liver enlargement, or both), increased discomfort, persistently low systolic blood pressure (below 80 mm Hg), fall in heart rate below 40 bpm, and appearance of atrioventricular block of second or third degree. 17 patients were not randomised because of intolerance to metoprolol for haemodynamic reasons—hypotension alone (in 3), hypotension plus extreme fatigue, increased congestive symptoms, or both (9), or the latter symptoms without hypotension (5). A further 17 patients tolerated the test dose but were not randomised because the ejection fraction was above 0·39 (6), the patient abused alcohol (1), had mental illness (1) or renal failure (1), or was unwilling to take part in the trial or could not be included for administrative reasons (8). Thus, 383 (92%) of all eligible patients were randomly assigned placebo (189) or metoprolol (194).

	Placebo (n=189)	Metoprolol (n=194)
% M/% F	75/25	70/30
Mean (SD; range) age in yr	49 (12; 16–71)	49 (12; 16–72)
Mean (SD; range) duration of heart failure (wk)	121 (130, 5–900)	127 (154; 1 069)
No (%) in NYHA functional class*		
Class I	4 (2)	6 (3)
Class II	89 (47)	82 (42)
Class III	88 (47)	98 (51)
Class IV	7 (4)	8 (4)
No (%) current smokers	32 (17)	39 (20)
Mean (SD; range) EF	0·22 (0·09; 0·04–0·42)	0·22 (0·08; 0·04–0·44)
Mean (SD; range) cumulative dose (g)	507 (250, 11–1706)	591 (287; 122 1440)
No (%) receiving concomitant treatment		
Digitalis	148 (79)	151 (78)
ACE inhibitors	154 (82)	150 (78)
Nitrates	25 (13)	27 (14)
Anti-arrhythmics	34 (18)	28 (14)
Frusemide†	137 (73)	152 (78)
Mean (SD) concentration		
Creatinine (μmol/L)	101 (28)	101 (23)
Potassium (mmol/L)	4·3 (0·4)	4·4 (0·4)
Sodium (mmol/L)	139 (5)	140 (4)
Mean (SD) haemodynamic variables at rest		
Heart rate (bpm)	91 (18)	90 (17)
Systolic BP (mm Hg)	118 (18)	118 (17)
Right atrial mean pressure (mm Hg)	6 (5)	6 (5)
PCWP mean (mm Hg)	17 (10)	17 (10)
Cardiac index (l. per min per m²)	2·6 (0·9)	2·5 (0·7)

EF = ejection fraction; BP = blood pressure; PCWP = pulmonary capillary wedge pressure.
*One patient was not classified according to NYHA.
†Mean (SD) dose 62 (77) and 63 (68) mg, respectively.

Table 1: Baseline characteristics of treatment groups

Patients were assigned to groups at each centre according to a computer-generated allocation list with a block size of 4. The randomisation was stratified by ejection fraction (below 0·20 and 0·20–0·39). Metoprolol was available in 5 mg and 50 mg tablets. The target dose was 100–150 mg daily, depending on body weight, age, heart rate, and blood pressure. Treatment started with a titration period; the daily dose increased over 6 weeks from week 1 10 mg, week 2 15 mg, week 3 30 mg, week 4 50 mg, week 5 75 mg, week 6 100 mg, and week 7 and onwards 150 mg. Doses were divided into two or three per day. Placebo was given in the same way. If the patient could not tolerate an increase in dose after a week, the previous dose could be kept for another week before dose increase. The highest dose tolerated during the titration period was used for the whole trial period.

The study period was 18 months for patients enrolled before Jan 1, 1990. At this time, when 211 patients had been enrolled, the follow-up protocol was simplified and the study period was shortened to 12 months. Patients were enrolled between September, 1986, and July, 1991.

Symptom-limited exercise (estimated with use of the Borg perceived exercise scale[19]) was done according to the modified Naughton protocol[20] in North American centres and according to a bicycle exercise protocol starting at 20 W with 10 W increment every min in the European centres. All exercise data were pooled in the analysis.

Right heart catheterisation was done when the patient had fasted overnight. Cardiac output was measured by thermodilution according to routines at each centre. Ejection fraction was measured by radionuclide angiography. A 26-item questionnaire about quality of life for patients with heart failure[21] was filled in by

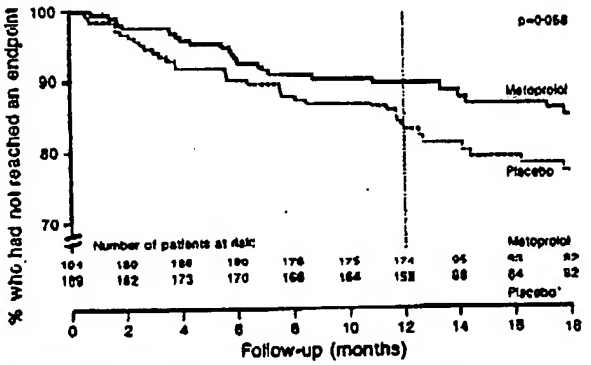

Figure 1: Likelihood of reaching a primary endpoint
211 patients were followed for 12 months and 172 for 18 months.

the patient. Follow-up investigations (including the quality of life questionnaire) were done at 45 days, 3 months, 6 months, 12 months, and 18 months. Exercise testing, right heart catheterisation, and measurement of ejection fraction were repeated at 6 and 12 months. So we could compare changes in NYHA classes, we created a class V for patients who had reached an endpoint.

We used a prospectively defined overall improvement index on which improvement was defined by two of the following three criteria: increase in exercise time of at least 25%; increase in ejection fraction by at least 0·07; and a fall in pulmonary wedge pressure by at least 20% combined with an increase in cardiac index by at least 15% if it was 2·4 L per min per m^2 or less. If the baseline pulmonary wedge pressure was below 12 mm Hg, only the criterion for cardiac index had to be satisfied. If the baseline cardiac index was more than 2·4 L per min per m^2, only the criterion for pulmonary wedge pressure had to be met. If a patient had both baseline pulmonary wedge pressure below 12 mm Hg and cardiac index above 2·4 L per min per m^2, only one of the two other conditions had to be met for the patient to be classified as improved.

Classification of primary endpoints was done by the endpoint committee, unaware of treatment. Death was classified as due to progressive heart failure or sudden, unexpected death (death within 1 h of new symptoms or found dead).

Hospital admissions and emergency room visits for heart failure or arrhythmias were assessed before the code was broken. The number of patients readmitted and the number of readmissions were recorded. Reasons for admission were classified by the investigators as progressive heart failure, arrhythmia, or other. The readmissions were reviewed by one member of the steering committee unaware of treatment.

Sample size calculations were based on an expected combined endpoint rate in the placebo group of 30% at 18 months' follow-up. We assumed that metoprolol would reduce the rate by 50%. For power of 90% a sample of 320 patients was required. Interim analysis of combined endpoint rate showed that 320 patients would provide too few endpoints and we decided in November, 1989, to extend the study.

	Placebo (n=189)	Metoprolol (n=194)	p
Total mortality/need for heart transplantation	38	25	0·058
Deaths	19	23	0·69
Progressive heart failure	5	5	0·92
Sudden cardiac death	12	18	0·36
Other vascular complications*	2	0	0·15
Need for heart transplantation	19	2	0·0001
Underwent transplantation or died while waiting	14	2	
Did not undergo transplantation†	5	0	

*Stroke, septicaemia.
†By Dec 1, 1992.

Table 2: Death or need for heart transplantation

	Mean (SD) ejection fraction		
	Placebo	Metoprolol	p
All patients	(n=104)	(n=111)	
Baseline	0·22 (0·09)	0·22 (0·08)	0·63
6 months	0·26 (0·11)	0·32 (0·13)	<0·0001
12 months	0·28 (0·12)	0·34 (0·14)	<0·0001
Baseline ejection fraction <0·20	(n=45)	(n=52)	
Baseline	0·14 (0·04)	0·14 (0·03)	0·42
6 months	0·20 (0·09)	0·27 (0·14)	0·007
12 months	0·23 (0·11)	0·31 (0·16)	0·008
Baseline ejection fraction 0·20–0·39	(n=59)	(n=59)	
Baseline	0·28 (0·05)	0·28 (0·06)	0·90
6 months	0·31 (0·10)	0·37 (0·11)	0·001
12 months	0·33 (0·10)	0·38 (0·11)	0·002

Table 3: Ejection fraction

The log-rank test[32] was used to test differences in the primary endpoint rate on an intention-to-treat basis. Fisher's permutation test[33] was used to test all other differences between the treatment groups. Tests for secondary endpoints were between-group comparisons. For variables measured at baseline and at 6 and 12 months the effect of treatment could be assessed by studying either the later values or the difference between them and baseline values. Calculation of the SD showed that the best analysis was with the difference from the baseline value for all variables except heart rate, right atrial mean pressure, and pulmonary capillary wedge mean pressure. Paired within-group comparisons were done for some of the secondary endpoint variables with the Wilcoxon signed rank test. The correlation between NYHA classification and quality of life was tested by Spearman's test. All p values are two-sided and not corrected for multiple comparisons.

Results

From September, 1986, to July, 1991, 383 patients were enrolled in the trial (placebo 189, metoprolol 194). The last subject completed 12 months of follow-up on July 31, 1992. Clinical characteristics, blood chemistry, haemodynamics at rest, and drug therapy at baseline were similar in the two treatment groups (table 1). The mean dose at 3 months after randomisation was 108 (SD 51) mg for metoprolol and 115 (SD 51) mg for placebo.

38 patients in the placebo group reached a primary endpoint (death or need for heart transplantation) compared with 25 in the metoprolol group (figure 1), a risk reduction of 34% (95% CI −6 to 62; p=0·058). 21 patients met the non-fatal endpoint of need for heart transplantation. 18 of the patients were actually listed for transplantation but 3 did not have the required medical insurance and were not listed. 2 of the 21 patients were in the metoprolol group and 19 in the placebo group (p=0·0001). Table 2 gives the outcome for all patients. 2 patients in the placebo group died after being listed for heart transplantation and 5 others had not undergone transplantation by Dec 1, 1992 (1 improved spontaneously and was removed from the transplant waiting list, 1 was lost to follow-up; 2 unable to pay for transplantation were treated openly with β-blockers and improved, and 1 was still awaiting transplantation).

The total number of deaths as first primary endpoint event was 23 in the metoprolol group and 19 in the placebo group. During the 12 or 18 months of follow-up, the all-cause mortality was 23 in the metoprolol group and 21 in the placebo group, since 2 subjects first classified as needing transplantation subsequently died. Of the 42 deaths, 30 (71%) were classified as sudden deaths.

Ejection fraction was measured at baseline and at 6 and 12 months in 215 patients (table 3). There was a significantly greater increase in ejection fraction in the metoprolol group

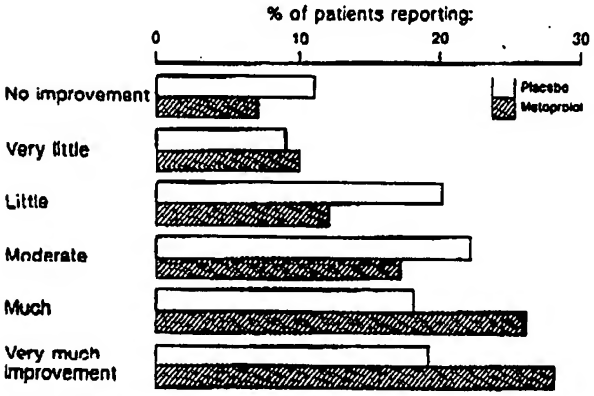

Figure 2: Assessment of quality of life in patients treated with placebo (n = 84) or metoprolol (n = 87) at 12 or 18 months' follow-up

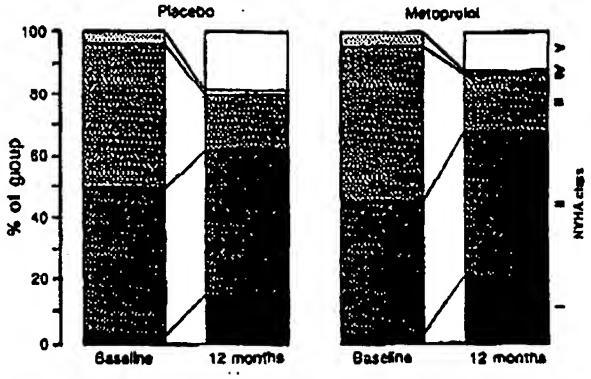

Figure 3: NYHA classification before and after 12 months' treatment with placebo or metoprolol

Class V = reached primary endpoint (death or need for heart transplantation).

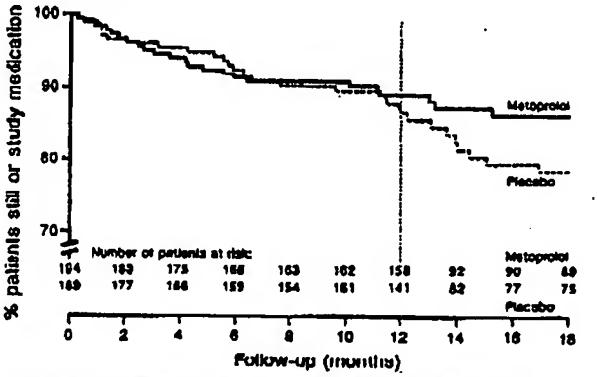

Figure 4: Percentage of patients still on study medication

than in the placebo group by 6 or 12 months' follow-up, overall and in both strata based on baseline ejection fraction. The improvement in myocardial function was similar whether or not patients were receiving concomitant treatment with ACE inhibitors, digitalis, or both.

Quality of life, assessed at the end of follow-up or the latest assessment before an endpoint was reached, improved significantly more in the metoprolol group than in the placebo group ($p = 0.01$, figure 2).

Within the metoprolol group, exercise capacity was significantly greater than at baseline at 6 months' follow-up (mean increase 80 [SD 216] s, $p = 0.0006$) and at 12 months (76 [214] s, $p = 0.0007$). In the placebo group, there was a significant improvement at 6 months (47 [189] s, $p = 0.007$) but not at 12 months (15 [178] s, $p = 0.46$). Thus, the difference between the groups in exercise capacity improvement was significant at 12 months (0.046) but not at 6 months.

In a subset of patients, resting haemodynamics were measured at 6 and 12 months (table 4). Heart rate and pulmonary wedge pressure decreased significantly more from baseline in the metoprolol group than in the placebo group, whereas systolic pressure, stroke volume, and stroke work index increased more in the metoprolol group. The improvement index based on ejection fraction, exercise time, and haemodynamics at rest showed improvement in 60% of metoprolol-treated patients at 12 months compared with 34% of the placebo group ($p = 0.009$).

There was a significant correlation between NYHA classification made by the physician and quality of life based on patient assessment ($p < 0.0001$). There was a significantly greater improvement in NYHA class from baseline to 12 months in metoprolol-treated than in placebo-treated patients (figure 3, $p = 0.01$).

Readmission to a hospital or emergency department for heart failure and arrhythmias was used as an index of morbidity. Investigator reported information was available for 177 (94%) placebo-treated patients and 184 (95%) metoprolol-treated patients. There was no difference between the groups in the number of patients readmitted (49 [28%] *vs* 37 [20%], $p = 0.12$) but the number of readmissions for all patients in the group was significantly lower with metoprolol treatment (83 *vs* 51) as was the mean number of readmissions per patient (0.47 [SD 0.98] *vs* 0.28 [0.67]; $p < 0.04$).

The definition of withdrawal was met when study medication was withdrawn more than 7 days before a subject reached a primary endpoint. By this definition, 54

	Placebo (n = 73)		Metoprolol (n = 74)		p for P vs M	Placebo (n = 72)		Metoprolol (n = 77)		p for P vs M
	Baseline	6 months	Baseline	6 months		Baseline	12 months	Baseline	12 months	
Heart rate (bpm)	90 (19)	84 (17)†	90 (19)	75 (14)*	0·0004	89 (18)	82 (14)†	89 (20)	77 (15)*	0·04
Systolic BP (mm Hg)	119 (18)	121 (17)	119 (15)	128 (22)†	0·03	120 (18)	121 (16)	119 (17)	132 (29)*	0·002
Right atrial mean pressure (mm Hg)	5·2 (4·0)	5·7 (5·1)	5·2 (3·9)	4·5 (3·8)	0·09	4·8 (3·8)	5·0 (3·9)	4·8 (3·6)	4·2 (3·6)	0·19
PCWP mean (mm Hg)	15·5 (9·1)	14·4 (10·3)	15·4 (9·2)	10·6 (7·5)*	0·01	15·4 (9·7)	13·1 (8·8)‖	15·6 (9·3)	10·7 (6·7)†	0·06
CI (L per min per m²)	2·7 (1·0)	2·7 (1·0)	2·5 (0·8)	2·8 (1·0)†	0·05	2·6 (0·9)	2·9 (1·1)‖	2·6 (0·9)	3·0 (1·1)†	0·36
SVI (mL per beat per m²)	31 (12)	35 (16)‖	30 (12)	38 (13)*	0·01	31 (11)	36 (16)‖	31 (12)	40 (15)*	0·10
SWI (g × m/m²)	32 (13)	39 (19)	30 (14)	42 (19)†	0·003	32 (13)	36 (18)	30 (14)	45 (21)*	0·0007
SVR (dyne s cm)	1358 (512)	1365 (518)	1426 (507)	1310 (518)‖	0·22	1310 (439)	1309 (453)	1429 (535)	1313 (498)‖	0·30

For differences within treatment group between baseline and follow-up value: *p < 0·0001, †p < 0·0001, ‡p < 0·01, §p < 0·05.
P = placebo; M = metoprolol; BP = blood pressure; PCWP = pulmonary capillary wedge pressure; CI = cardiac index; SVI = stroke volume index; SWI = stroke work index; SVR = systemic vascular resistance.

Table 4: Effects of haemodynamics at rest at 6 and 12 months' follow-up (mean [SD] values)

patients discontinued study medication (figure 4; 23 metoprolol, 31 placebo). The reason for withdrawal was progressive heart failure in 7 metoprolol-group and 13 placebo-group patients ($p=0\cdot14$), non-compliance or administrative difficulties in 12 and 11 ($p=0\cdot96$) respectively, and other adverse events in 4 and 7 ($p=0\cdot32$). Adverse events thought to be related to β-blockers were the reason for withdrawal for 1 metoprolol patient and 3 placebo recipients. During the titration phase, only 11 patients were withdrawn (5 metoprolol, 6 placebo). If we include patients whose medication was withdrawn during the 7 days before they reached a primary endpoint, more patients were withdrawn from the placebo group.

Discussion

Despite the substantial reduction in the number of patients in this study who deteriorated clinically to the point of requiring heart transplantation, metoprolol had no effect on all-cause mortality. It is possible that there were too few deaths for the trial to detect an effect or that because of the trial design patients with the highest risk of death were placed on a waiting list for heart transplantation. Furthermore, the patients were on optimum drug treatment for heart failure, including ACE inhibitors, which has been shown to decrease long-term mortality.[24,25] At the time of Swedberg et al's study,[4] which showed a reduction in mortality with β-blockers, neither heart transplantation nor ACE-inhibitor treatment was available; these factors may explain the high mortality in their control group and the ability to detect an effect of β-blockers on survival. Although it remains possible that β-blockers prevent death in idiopathic dilated cardiomyopathy, an even larger trial is needed to resolve this issue and to investigate the cause of death in subjects with heart failure.

The mean age of the patients in this trial was lower than that in other heart failure trials.[24,25] This factor may explain why as many as 33% of patients who had deteriorating heart failure were listed for heart transplantation. Of the deaths, 71% were classified as unexpected sudden death and 29% as progressive heart failure, probably because most of the patients with progressive dysfunction first reached the non-fatal endpoint, need for heart transplantation.

Our findings on improvement in cardiac function accord with several previous reports.[2,11-18] We did not find, by contrast with previous studies,[11,17] any change in cardiac index; this discrepancy may be due to selection of patients with lower cardiac output in the previous studies.

Engelmeier et al[13] reported that treatment with metoprolol increases exercise capacity in patients with congestive heart failure due to idiopathic dilated cardiomyopathy. Similarly, we found that metoprolol was associated with a significant increase in exercise duration. The use of our improvement index based on substantial changes in important clinical variables allowed us to detect an improvement in the metoprolol group that would not have been apparent from changes in mean values alone. The improvement of 34% in the placebo group is consistent with previously reported spontaneous improvement in patients with idiopathic dilated cardiomyopathy.[26]

Although β-blockers have been tested in the setting of heart failure from idiopathic dilated cardiomyopathy for 20 years, no mechanism for the consistent improvement in myocardial function is clear. Up-regulation of β-adrenergic receptors after long-term β-blockade[13,15] could facilitate the contractile response to sympathetic stimulation during exercise and thus lead to improved exercise tolerance. Reduction in metabolic stress, secondary to lowering of heart rate, could improve myocardial energy balance and thus enhance the recovery of the failing myocardium.[17] The presence of autoantibodies against the β_1-receptor in about 33% of patients with idiopathic dilated cardiomyopathy[27] may account for a chronic positive chronotropic effect beyond that caused by adrenergic stimulation, and this effect could be attenuated by β-blockers. Finally, an antiarrhythmic effect of β-blockade might be important in heart failure; however, we found no effect of metoprolol on the incidence of sudden death.

Improvement in myocardial function with metoprolol was not affected by concomitant treatment with ACE inhibitors, which suggests that the two types of drug produce improvement by different mechanisms. Although some degree of sympathetic blockade is achieved by ACE inhibitors (decrease in heart rate and serum noradrenaline concentratione), the sympatholytic effect of ACE inhibition is not as complete as that possible with β-blockers.[28] More pronounced neuroendocrine activation with higher concentrations of catecholamines, renin-angiotensin-aldosterone, and atrial natriuretic peptide is seen in patients with the worst prognosis.[29] The favourable effects of β-blockade in our study are consistent with the general hypothesis that excessive neuroendocrine activation may be detrimental.[30] Since the degree of neuroendocrine activation is a strong predictor of mortality,[29] the combination of an ACE inhibitor and a β-receptor-blocking agent might provide the best treatment of heart failure due to dilated cardiomyopathy.

We must emphasise that the observed beneficial effects after metoprolol treatment apply only to patients with symptomatic idiopathic dilated cardiomyopathy and ejection fraction below 0·40 who met the strict criteria defined in our study protocol; these include a test dose and careful titration of metoprolol. With these reservations, however, we conclude that low doses of the drug are well tolerated. Beneficial effects of β-blocker treatment may be found in patients with other forms of congestive heart failure. For example, patients with ischaemic cardiomyopathy also show a good response to β-blockers.[17,18] However, a large, prospective study is also needed for those patient groups.

We thank Dr B Andersson, for generating program software and data handling, Ms E Lavik Olofsson, Ms M Scharin Täng, Ms I Eurenius, and Ms G Fritzon for data collection, Mr T Karlsson for statistical help, Ms E Claus for preparation of the paper, and Astra Hässle AB, Mölndal, Sweden, Astra GmbH, Linz, Austria, Astra Chemicals GmbH, Wedel, Germany, Astra Pharmaceutica BV, Rijswijk, Netherlands, Ciba-Geigy Corporation, USA, Swedish Heart Lung Foundation, and Swedish Medical Research Council for support.

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ATTACHMENT D

A Randomized Trial of β-Blockade in Heart Failure

The Cardiac Insufficiency Bisoprolol Study (CIBIS)

CIBIS Investigators and Committees

Background Functional benefit in heart failure due to idiopathic dilated cardiomyopathy has been observed after β blockade, but improvement in survival has not been established in a large-scale randomized trial. This was the main objective of the Cardiac Insufficiency Bisoprolol Study (CIBIS).

Methods and Results Six hundred forty-one patients with chronic heart failure of various etiologies and a left ventricular ejection fraction of <40% entered this placebo-controlled, randomized, double-blind study. Patients were in New York Heart Association functional class III (95%) or IV (5%) at inclusion. All received background diuretic and vasodilator therapy (an angiotensin-converting enzyme inhibitor in 90% of cases). A total of 320 patients was randomized to bisoprolol and 321 to placebo. Mean follow-up was 1.9 years. Bisoprolol was well tolerated without between group difference in premature treatment withdrawals (82 on placebo, 75 on bisoprolol; NS). The observed difference in mortality between groups did not reach statistical significance: 67 patients died on placebo, 53 on bisoprolol ($P=.22$; relative risk, 0.80; 95% confidence interval, 0.56 to 1.15). No significant difference was observed in sudden death rate (17 on placebo, 15 on bisoprolol) or death related to documented ventricular tachycardia or fibrillation (7 on placebo, 4 on bisoprolol). Bisoprolol significantly improved the functional status of the patients; fewer patients in the bisoprolol group required hospitalization for cardiac decompensation (90 on placebo versus 61 on bisoprolol, $P<.01$), and more patients improved by at least one New York Heart Association functional class (48 on placebo versus 68 on bisoprolol, $P=.04$) by the end of follow-up period.

Conclusions These results confirm previous trials evidence that a progressively increasing dose of β-blocker in severe heart failure confers functional benefit. Subgroup analysis suggested that benefit from β-blockade therapy was greater for those with nonischemic cardiomyopathy. However, improvement in survival while on β-blockade remains to be demonstrated. (*Circulation*. 1994;90:1765-1773.)

Key Words • clinical trials • β-blockers • heart failure • bisoprolol • CIBIS

Sympathetic activation in chronic heart failure may have deleterious consequences, including an accelerated mortality rate. β-Blockade therapy may provide some cardioprotection and has been advocated for patients with idiopathic dilated cardiomyopathy and chronic heart failure.[1] While some small-scale trials with β-blocking drugs were negative,[2] recent studies have proven improved cardiac function and associated heart failure symptoms.[3-5] However, improved survival by β-blockade in patients with congestive heart failure has not been conclusively demonstrated in a large-scale, placebo-controlled study.

We thus initiated a placebo-controlled, randomized, double-blind trial with bisoprolol (β_1-selective adrenergic receptor antagonist) to, first, evaluate the impact of such treatment on mortality in patients with heart failure of various etiologies and, second, assess the tolerability of β-blockade in established heart failure. Although most studies with β-blocking drugs have concentrated on idiopathic dilated cardiomyopathy, we also wanted to examine the actions of β-blockade on heart failure of ischemic origin. The study rationale and protocol have been described.[6]

Received March 30, 1994; Revision accepted July 12, 1994.

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Methods

Study Design

The Cardiac Insufficiency Bisoprolol Study (CIBIS) trial was a double-blind, placebo-controlled, randomized, multicenter European trial that compared two parallel groups of patients who had chronic heart failure. The primary end point was mortality. Secondary end points were the tolerability of bisoprolol and analysis of all critical events.

To achieve a study power of 90%, we estimated that 1200 patient-years of observation would be required to demonstrate a reduction of 33% in mortality for bisoprolol compared with placebo, provided that the 2-year mortality rate in the placebo group was between 36% and 38% and the α risk was 5% (two-sided log-rank test).

Inclusion Criteria

To be included in the study, patients had to fulfill the following criteria: age between 18 and 75 years, chronic heart failure with or without sinus rhythm, and dyspnea or fatigue corresponding to New York Heart Association functional class III or IV. Patients had to be ambulatory and not awaiting cardiac transplantation. Mandatory background medication was diuretic and vasodilator therapy. Left ventricular ejection fraction (isotopic or angiographic performed within 4 weeks before randomization) had to be <40%. Etiology of heart failure was defined as (1) idiopathic dilated cardiomyopathy when no known cause of cardiomyopathy could be found, (2) ischemia when typical history of coronary artery disease, history of myocardial infarction, or presence of significant (>70%) coronary artery stenoses had been documented, (3)

hypertension when history of established hypertension or antihypertensive therapy was present, and (4) valvular heart disease: patients with primary valvular disease (that had to be surgically repaired for at least 6 months) and patients with nonischemic dilated cardiomyopathy associated with a significant mitral valve insufficiency were classified in this last group of etiology.

Clinical stability was a prerequisite before inclusion and was defined as the absence of any episode of heart failure decompensation during the 6-week period before study entry and the absence of major modification of heart failure therapy in the previous 3 weeks.

Noninclusion Criteria

Exclusion criteria included heart failure due to hypertrophic or restrictive cardiomyopathy with predominant left ventricular diastolic dysfunction, heart failure secondary to mitral or aortic valve disease that was not surgically repaired or had been surgically repaired for less than 6 months, patient with coronary heart disease awaiting bypass surgery or a recent history of myocardial infarction (less than 3 months), patients already on a heart transplantation waiting list, nonambulatory patient with disabling permanent dyspnea at rest, insulin-dependent diabetes, asthma, renal insufficiency (plasma creatinine >300 μmol/L), hypothyroidism or hyperthyroidism, patient whose life expectancy was shortened by a severe illness such as a malignant disease, or patient with a resting heart rate <65 beats per minute or with a systolic blood pressure of <100 mm Hg or >160 mm Hg immediately before randomization.

Study Medications

Allocation to randomized therapy was centrally controlled by computerized interrogation and stratified by center. Study treatment was titrated and administered blindly using divisible 2.5-mg pills and matched placebo. The initial dose was 1.25 mg/d, increased 48 hours later to 2.5 mg/d and 1 month after to 5 mg/d. Study treatment initiation and dose increments were performed during hospitalization for periods between 2 and 6 days. Dose increment was not a forced titration procedure; each investigator was free, according to the clinical status of the patient, to either follow the recommended dose increment or remain at one of the following dose levels: 1.25, 2.5, 3.75, or 5 mg/d.

Associated Treatments

All patients had to receive baseline diuretic and vasodilator therapy (angiotensin-converting enzyme inhibitors were recommended). Digitalis and amiodarone could be administered if these medications were not initiated within 6 weeks before inclusion or within 2 months after inclusion. Prohibited intercurrent medications were β-adrenergic agonist or antagonist drugs and phosphodiesterase inhibitors. Only calcium antagonists of the dihydropyridine type were permitted (especially for ischemic patients). However, the administration of calcium antagonist was not recommended as a general policy.

Patient Follow-up and Assessment of Compliance

After titration, all patients were followed by investigators every 3 months until the end of the study according to the intent-to-treat principle. All critical events, cardiovascular and noncardiovascular, were to be reported to the investigators. To avoid any influence on nonmortality end points, all critical events were blinded as well as independently analyzed and adjudicated on by the Critical Events Committee (based on detailed description collected on site by the study monitors).

Compliance with study treatment was assessed by pill count and by investigator assessment using a semiquantitative scale. At each follow up visit, compliance with study treatment was classified by the investigator as <10%, 10% to 50%, 50% to 90%, or >90%.

Outcome Analysis

The main end point was total mortality. The causes of death was adjudicated on by the Critical Events Committee using the following classification: sudden death, progressive pump failure, myocardial infarction, cardiogenic shock, documented ventricular tachycardia or fibrillation, other cardiovascular causes, and etiologies that were uncertain despite detailed investigation. Sudden death was defined as death occurring within 1 hour without previous worsening of symptoms and without documented ECG or Holter recording of ventricular tachycardia (defined by occurrence of more than three consecutive premature beats) or fibrillation.

In addition, the circumstances of death were classified as (1) instantaneous death or (2) death within 1 hour of new symptoms or (3) death after 1 hour after clinical deterioration, and (4) unwitnessed death.

Bisoprolol tolerability, the secondary end point, was assessed by analyzing the number of premature treatment withdrawals, the functional status of each patient (New York Heart Association functional class), and the number of nonlethal critical events. The latter included all cardiovascular and noncardiovascular events.

Statistical Analysis

Data analyses were performed using SAS software on an intent-to-treat basis on all randomized patients.

Baseline characteristics and other follow-up variables were compared between groups using a χ^2 test or Fisher's exact test for categorical variables and Student's t test for continuous variables. Comparisons of blood pressure and heart rate measurements, which were repeated during follow-up, were performed by variance analysis for repeated measurements.

Survival curves were established using the Kaplan-Meier life table. Comparison between the two treatment groups was performed using the log-rank test. The significance level for overall mortality was set at .05. Adjustment for two interim analyses was done with the O'Brien and Fleming multiple-testing procedure.[7]

The Cox proportional hazards model was used to assess the relative risk between the two treatment groups and association of variables with survival. The continuous variables were dichotomized in two groups around the median value in the multivariate model to allow calculation of relative risks for comparison with discrete variables.

For subgroup analysis of survival, a Breslow-Day test for homogeneity of the odds ratios was used to compare differences between treatments among subgroups.

All quantitative results are expressed as mean±95% confidence interval of the mean. All P values are two-sided.

Study Organization

Inclusion occurred between March 1989 and August 1992. Last follow-up visits took place between December 1992 and February 1993. Seventy centers in nine European countries participated in the study. All investigators and members of the different committees are listed in the "Appendix."

Results

Study Population

Six hundred forty-one patients were included in the study: 321 in the placebo group and 320 in the bisoprolol group. Six hundred nine patients (95%) were in New York Heart Association functional class III, and 32 (5%) were in class IV at inclusion.

Among all baseline parameters recorded from clinical examination of the patient (history of heart failure,

physical examination) and ECG (Table 1), only two differed between the treatment groups: the number of patients with a history of myocardial infarction was higher in the bisoprolol group compared with the placebo group ($P=.005$), and diastolic blood pressure was higher in the bisoprolol group ($P=.03$). However, due to the multiplicity of comparisons of baseline data, these differences may have occurred by chance alone.

Coronary angiography was available in 351 patients (55%). Among them, significant coronary stenosis were reported in 92 of 172 patients (53%) in the placebo group and in 103 of 179 patients (57%) in the bisoprolol group (NS).

Ventricular function parameters at inclusion are given in Table 1. No differences between groups were present. The only biological parameter recorded at inclusion was natremia: 139.2±0.4 mmol/L in the placebo group and 139.4±0.4 mmol/L in the bisoprolol group (NS).

Associated treatments are listed in Table 1. All patients had to receive both a diuretic and a vasodilator (in 90% of patients, this was an angiotensin-converting enzyme inhibitor).

Follow-up Assessment

Follow-up Duration, Compliance, and Dose

Mean duration of follow-up was 1.9±0.1 years. All patients, including premature withdrawals, were followed until the end of the study. Only one was lost to follow-up. Compliance was similar in each group where the estimated proportion of study treatment taken was >50% in >90% of all patients and >90% in 67% of the patients in the bisoprolol group and in 70% of them in the placebo group. An indirect index of good compliance was provided by heart rate reduction for bisoprolol versus placebo. At the end of the titration period (1 month after the last dose increment), a mean heart rate reduction of 15.7±1.7 beats per minute (19% reduction) was observed for bisoprolol, which was maintained throughout the follow-up period without any significant change in the placebo group (Fig 1). At that time, the mean administered daily dose for patients still receiving study treatment was 4.5±0.1 mg with placebo and 3.8±0.2 mg with bisoprolol ($P<.0001$). Fifty-nine percent of patients in the bisoprolol group and 82% in the placebo group received the 5-mg daily dose ($P<.0001$).

The dose level of study treatment, evaluated at the last follow-up visit of the study or at the last visit before premature withdrawal of study treatment, was as follows in the bisoprolol group: 17.3% of patients received 1.25 mg/d, 29.5% received 2.5 mg, 2% received 3.75 mg, and 51% received 5 mg.

Protocol Violations

Thirty-eight protocol violations were recorded, 26 at inclusion and 12 during the follow-up period. They were equally distributed between the treatment groups. Violations at inclusion were ejection fraction of >40% (one case, with ejection fraction of 44%), clinical or therapeutic instability during the preinclusion period (n=14), severe life-threatening associated disease (n=2), and unauthorized treatments (n=9).

During follow-up, there were unauthorized concomitant treatments (n=6), unjustified CIBIS treatment discontinuation (n=5), and CIBIS treatment started at a higher-than-recommended dose (n=1).

Protocol End Points

Survival

Bisoprolol did not significantly reduce mortality. Sixty-seven deaths (20.9%) occurred in the placebo group compared with 53 deaths (16.6%) in the bisoprolol group. Comparison of these survival curves with the log-rank test reached a value of $P=.22$ (Fig 2). Relative risk of death calculated using Cox regression (bisoprolol versus placebo) was 0.80 with a 95% confidence interval of 0.56 to 1.15.

The cause and circumstances of death are listed in Table 2. No difference in mode of death occurred between the two groups: sudden, 26.7%; death related to a documented ventricular tachycardia or fibrillation, 9.2%; and instantaneous, 14.2%. However, when sudden deaths and deaths with documented ventricular tachycardia or fibrillation were pooled (some sudden deaths are related to ventricular arrhythmias), 24 of such deaths occurred in the placebo group and 19 occurred in the bisoprolol group. This 20% reduction is similar to the overall mortality reduction in bisoprolol group regardless of etiology of death.

All instantaneous deaths were included in sudden deaths (n=14) or deaths related to documented ventricular arrhythmias (n=3). Amiodarone treatment did not significantly modify the proportion of sudden deaths or deaths related to documented ventricular arrhythmias: 14 (47%; 11 sudden) deaths occurred among 30 patients who died while receiving amiodarone, whereas 29 (32%; 21 sudden) occurred among 90 patients who died while not receiving amiodarone.

Premature Treatment Withdrawals

Study treatment was prematurely withdrawn in 82 patients in the placebo group (26%) and 75 in the bisoprolol group (23%, NS) with a respective mean of 257±57 and 255±67 days after inclusion (NS). The reasons for early treatment withdrawal were equally distributed in each group. Treatment failure or intercurrent pathological events (cardiovascular and noncardiovascular) were the most frequent cited reasons for early premature treatment withdrawal: heart failure deterioration and/or being in a pretransplantation program were recorded in 57 cases as the cause of premature treatment withdrawal. Two cases of sinus bradycardia and 2 cases of atrioventricular blockade were recorded in the bisoprolol group and led to premature withdrawal of treatment.

Kaplan-Meier survival curves restricted to patients with a premature treatment withdrawal and starting at the time of withdrawal were similar in both groups (log-rank test, NS).

Among these 157 study treatment withdrawals, 31 were recorded during the first month after inclusion: 13 in the placebo group and 18 in the bisoprolol group (NS).

Nonlethal Critical Events and Evolution of Functional Status

Apart from death and premature treatment withdrawal, a total of 524 critical events occurring in 268 patients were recorded and validated (Table 3). Signif-

TABLE 1. Population Characteristics at Inclusion

	Placebo (n=321)	Bisoprolol (n=320)
Age, y	59.2±1.1	60.1±1.2
Sex, n		
Male	265 (83%)	264 (82.5%)
Female	56 (17%)	56 (17.5%)
New York Heart Association functional class, n		
III	304 (95%)	305 (95%)
IV	17 (5%)	15 (5%)
Etiology of heart failure		
Idiopathic dilated cardiomyopathy	115 (36%)	117 (36.5%)
Ischemia	170 (53%)	180 (56%)
Hypertension	19 (6%)	15 (5%)
Valvular disease	17 (5%)	8 (2.5%)
Delay between onset of first symptoms and inclusion, y	3.2±0.4	3.2±0.4
History of acute episodes of heart failure, n	185 (58%)	173 (54%)
History of myocardial infarction, n	134 (42%)	169 (53%)†
History of angina, n	111 (35%)	123 (38%)
Systolic blood pressure, mm Hg	125.6±1.5	127.7±1.7
Diastolic blood pressure, mm Hg	77.9±1.0	79.5±1.0*
Heart rate, bpm	82.5±1.6	82.8±1.5
Patients in atrial fibrillation, n	45 (14%)	40 (12.5%)
Presence of ventricular arrhythmias on standard 12-lead ECG, n‡	72 (22%)	59 (18%)
LV ejection fraction, %	25.8±0.9	25.0±0.9
Cardiothoracic ratio (chest radiograph), %	54.7±0.7 (n=276)	54.9±0.7 (n=281)
Echocardiography parameter	(n=316)	(n=315)
LV end-diastolic diameter, cm	6.7±0.1	6.7±0.0
LV end-systolic diameter, cm	5.6±0.1	5.5±0.1
LV fractional shortening, %	17.0±0.7	17.3±0.8
Diuretic, n	321 (100%)	320 (100%)
Vasodilator, n	321 (100%)	320 (100%)
ACE inhibitor	291 (91%)	284 (89%)
Calcium antagonist (dihydropyridine type)	22 (7%)	16 (5%)
Other vasodilator	128 (40%)	131 (41%)
Digitalis, n	181 (56%)	183 (57%)
Antiarrhythmic drug, n		
Amiodarone	60 (19%)	66 (21%)
Other	19 (6%)	22 (7%)
Anticoagulant, n	121 (38%)	132 (41%)
Antiplatelet, n	88 (27%)	78 (24%)

LV indicates left ventricular; ACE, angiotensin-converting enzyme.
Results are expressed as mean±95% confidence interval of the mean.
‡One or more ventricular premature beats on standard 12-lead ECG.
*P=.03; †P<.005 vs placebo.

icantly fewer patients in the bisoprolol group had at least one episode of heart failure decompensation (with or without acute pulmonary edema) requiring hospitalization (61 versus 90, P<.01).

Combining all nonlethal events that can be considered to be directly related to pump failure (acute pulmonary edema, heart failure without pulmonary edema, and cardiogenic shock), we recorded 154 epi-

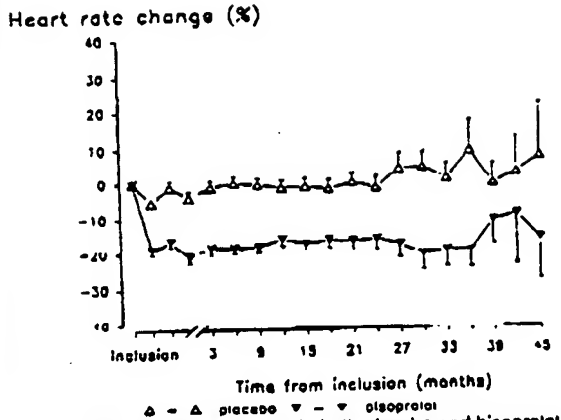

Fig 1. Plot of heart rate change in both placebo and bisoprolol groups during follow-up period. Bars represent limits of the 95% confidence interval of the mean.

sodes in the placebo group (0.48 per patient) and 107 in the bisoprolol group (0.33 per patient) ($P<.001$).

Documented ventricular tachycardia (defined by occurrence of more than three consecutive ventricular premature beats) or fibrillation were recorded in 11 patients receiving placebo and 3 receiving bisoprolol ($P=.03$), yielding a total of 14 and 5 events, respectively (Table 3).

More patients improved their functional status while receiving bisoprolol than did those receiving placebo: at the end of follow-up, compared with the functional status at inclusion, an improvement of at least one New York Heart Association functional class was found in 68 patients (21%) in the bisoprolol group and 48 patients (15%) in the placebo group ($P<.03$). In addition, a similar proportion of patients in each group had a similar deterioration of their functional status (loss of one functional class, 41 [13%] for bisoprolol versus 35 [11%] for placebo [NS]).

Adjustment of Mortality and Event Rates

The effect of study treatment was adjusted with a proportional hazards Cox model. The baseline variables that were independent predictors of death were systolic blood pressure ($P=.0001$), New York Heart Association

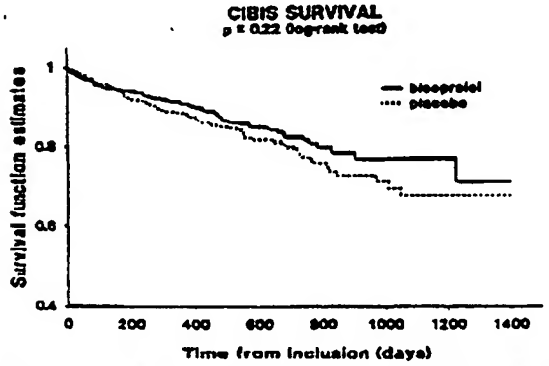

Fig 2. Survival curves (Kaplan-Meier) in CIBIS patients (n=641): 67 patients died receiving placebo, and 53 died receiving bisoprolol. Risk reduction on bisoprolol: 0.80 (95% confidence interval=0.56–1.15).

Table 2. Number, Cause, and Circumstances of Death

	Placebo	Bisoprolol	Total
Deaths, n	67	53	120
Alive, n	254	267	521
Cause of death			
Sudden death	17	15	32
Heart failure	22	11	33
Myocardial infarction	0	1	1
Cardiogenic shock	7	2	9
Documented VT or VF	7	4	11
Other cardiovascular cause	6	7	13
Noncardiovascular cause	4	3	7
Impossible to classify	4	10	14
Circumstance of death			
Instantaneous death	9	8	17
Death within 1 hour	17	11	28
Death after 1 hour	33	19	52
Unwitnessed death	8	15	23

VT indicates ventricular tachycardia; VF, ventricular fibrillation.

functional class ($P=.0018$), age ($P=.0015$), left ventricular ejection fraction ($P=.011$), and presence of arrhythmias on 12-lead ECG ($P=.066$). This adjustment did not change the P value for the treatment effect.

When death and nonlethal events (heart failure decompensation episode, cardiogenic shock, transplantation) are combined, the baseline variables that were independent predictors of these events are study treatment ($P=.04$), New York Heart Association functional class ($P=.0001$), systolic blood pressure ($P=.0003$), age ($P=.005$), left ventricular ejection fraction ($P=.012$), presence of arrhythmias on 12-lead ECG ($P=.03$), and ventricular rate >80 beats per minute ($P=.07$).

Subgroup Analyses

Two main subgroup analyses were postulated as being of therapeutic interest; these subgroups were determined according to baseline New York Heart Association functional class and to the etiology of heart failure.

In patients with New York Heart Association functional class IV, 10 of 17 (59%) died on placebo versus 4 of 15 (27%) on bisoprolol (log-rank test, $P=.054$). In New York Heart Association functional class III, 57 of 304 patients (19%) died on placebo and 49 of 305 (16%) on bisoprolol (NS). Breslow Day test for homogeneity of odds ratio did not achieve a significant P value.

We found a significant difference in the response to bisoprolol between patients with or without a history of myocardial infarction. Among 303 patients with a history of myocardial infarction, 25 of 134 patients (19%) died on placebo compared with 35 of 169 (21%) on bisoprolol (log-rank test, $P=.55$, NS, Fig 3a). However, among 338 patients without a history of myocardial infarction, 42 of 187 patients (22.5%) died on placebo and 18 of 151 (12%) died on bisoprolol (log-rank test,

TABLE 3. Nonlethal Critical Events

	Placebo	Bisoprolol	Total
Heart failure			
Acute pulmonary edema	40	29	69
Heart failure without acute pulmonary edema	111	78	189
Cardiogenic shock	3	0	3
Ventricular tachycardia or fibrillation	14	5	19
Atrial fibrillation or PSVT	14	13	27
Bradycardia <40/min	2	8	10
Second- or third-degree atrioventricular block	0	2	2
Hypotension	3	5	8
Myocardial infarction	2	2	4
Other cardiovascular events			
Pulmonary embolism	1	0	1
Stroke	7	6	13
Other systemic embolisms	1	1	2
Resuscitated cardiac arrest	1	1	2
Pregraft work-up	9	4	13
Transplantation	6	3	9
Other	29	26	55
Total cardiovascular events	243	183	426
Noncardiovascular events	54	44	98
Total	297	227	524

PSVT indicates paroxysmal supraventricular tachycardia. The total of 524 nonlethal critical events has been recorded on a total number of 268 of 641 included patients (several critical events have occurred for the same patient).

P=.01, Fig 3b). Breslow Day test for homogeneity of the odds ratio was significant (P=.034).

When subgroup analysis focused on heart failure etiology according to investigator diagnosis, log-rank test on survival between study treatment groups provided the following results: P=.94 in patients with ischemia (n=350) and P=.06 without ischemia (29 of 151 patients died on placebo and 17 of 140 on bisoprolol). In patients with idiopathic dilated cardiomyopathy as the unique diagnosis, 23 of 115 died on placebo and 11 of 117 died on bisoprolol (P=.01). Presence of angina did not significantly influence bisoprolol effects on survival.

Discussion

The primary objective of CIBIS was to test on an intent-to-treat basis the hypothesis that bisoprolol-induced β-blockade could reduce mortality compared with placebo in patients with chronic heart failure. The 20% observed mortality risk reduction for bisoprolol after a mean follow-up period of almost 2 years was not statistically significant at the 5% level. However, the 95% confidence interval of this reduction remains compatible with a significant reduction in mortality.

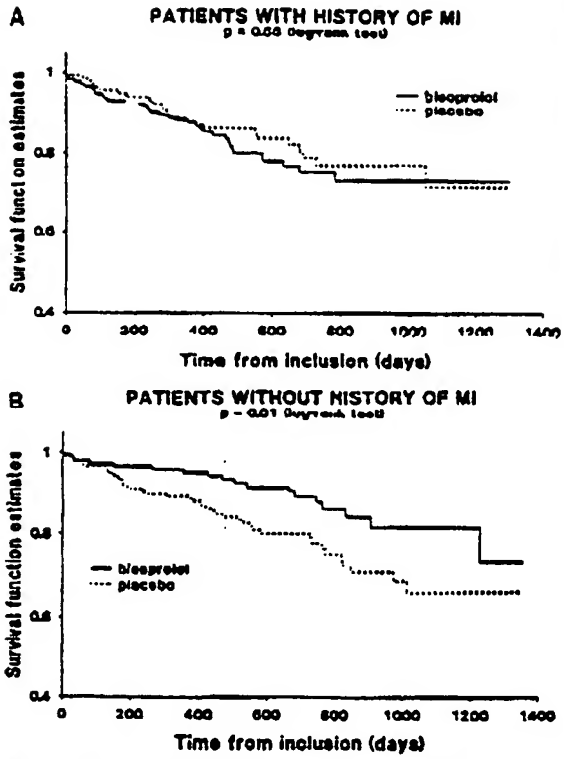

FIG 3. A, Survival curves (Kaplan-Meier) in CIBIS patients with history of myocardial infarction (n=303): 25 of 134 patients died receiving placebo, and 35 of 169 died receiving bisoprolol. B, Survival curves (Kaplan-Meier) in CIBIS patients without history of myocardial infarction (n=338): 42 of 187 patients died receiving placebo, and 18 of 151 died receiving bisoprolol.

No previous trials have tested the effects of β-blockade on mortality with the exceptions of the MDC trial[5] and the present CIBIS study. The MDC trial end point, however, was a combined end point. Therefore, the CIBIS trial was the first large-scale trial testing β-blockade in heart failure with mortality as main end point.

The lower-than-expected background mortality rate reduced the power of the study, which was based on an expected mortality rate in the placebo group between 36% and 38%. To achieve such a mortality rate, a higher recruitment rate of New York Heart Association functional class IV patients was initially planned. The proportion of class IV patients was very low (5%) and may be related to either the restrictive study inclusion of ambulatory patients or investigator reluctance to expose patients with advanced heart failure to β-blockade.

The 2-year mortality rate of 20% in the CIBIS placebo group was similar to that of the enalapril-treated groups in the SOLVD study[6] and the Ve-HeFT II trials.[9] In these trials, however, the majority of included patients were in New York Heart Association functional class II or III. Ischemic patients represented half of the patients in V-HeFT II as in CIBIS but 72% in SOLVD. In other trials, such as the Promise study,[10] among the class III heart failure placebo patients (who were on receiving angiotensin-converting enzyme inhibitors), there was an estimated mortality rate of 30%-at 1 year. It appears, then, very likely that some of the

CIBIS patients were closer to class II than to class III. They were, however, considered by investigators as class III patients at inclusion. In effect, the CIBIS trial tested the benefit of the addition of β-blockade to standard heart failure therapy (diuretic and angiotensin-converting enzyme inhibitors) in ambulatory patients who were symptomatic despite conventional therapy.

Only half of the patients received the target dose of 5 mg bisoprolol. Thus, another reason for failure to reach statistical difference between the groups may have been suboptimal dosing of medication. The optimal level of β-blockade relative to the goals of mortality reduction remains to be established. With bucindolol, Dristow et al[11] observed an increase in ejection fraction only with the highest dose. The nature of the relation between the hemodynamic effects and survival improvement with β-blockade in heart failure is unknown.

Although CIBIS failed to demonstrate a significant reduction of mortality with bisoprolol, the functional status of patients was significantly improved by bisoprolol compared with placebo. Fewer patients (31% reduction) had at least one episode of heart failure decompensation requiring hospitalization in the bisoprolol group and more patients improved clinically by at least one New York Heart Association functional class over the study period. In addition, a similar proportion of patients in each group presented a loss of one functional class, suggesting that the course of the disease was not worsened by bisoprolol compared with placebo.

These results confirm those of previous controlled and uncontrolled trials that found functional as well as hemodynamic improvement following β-blockade treatment.[3,6,12-14] We did not observe a significant reduction in heart transplantations in the β-blockade–treated group, as was found in the MDC trial.[5] However, the transplantation rate in our study was lower (1.4%) than in the MDC trial (5.5%). A possible explanation for the difference in transplantation rate is that in the MDC trial all patients were idiopathic and much younger (average of 10 years younger).

Tolerability to progressive bisoprolol titration according to the chosen schedule was quite satisfactory. Indeed, premature treatment withdrawal was almost identical in the two groups (26% for placebo and 23% for bisoprolol), with one fifth occurring during the titration period. The most frequent reason for premature treatment withdrawal was treatment failure. In such cases, the investigator decision to stop study treatment was generally based on ethical considerations in the face of clinical evidence of heart failure deterioration.

Progressive increase of β-blocking doses appears to be an important factor allowing hemodynamic and functional benefit in patients with heart failure. Previous studies have clearly shown that improvement in ejection fraction takes several months to develop.[3,16] In contrast, nonprogressive administration of antihypertensive doses of β-blockade can lead to hemodynamic as well as functional status deterioration.[17] In the CIBIS study, patients were not selected according to tolerance of a test dose of bisoprolol. This was done to avoid selection of a population uniquely responsive to β-blockade and restriction of the applicability of the findings of the study.

Despite the absence of significant benefit in mortality for the entire population, subgroup analysis according to etiology of heart failure was of interest. The enhanced action of bisoprolol in patients without ischemia, in the absence of a history of myocardial infarction or in patients with an idiopathic dilated cardiomyopathy, was tantalizing. However, no stratification based on etiology of heart failure was performed at randomization excluding valid separate analysis according to these subgroupings. Therefore, results of subgroup analysis can be considered only suggestive, and differential results of bisoprolol efficacy according to etiology must await further formal studies.

It should, however, be noted that the extent of mortality reduction achieved with bisoprolol (50% reduction) versus placebo in patients without a history of myocardial infarction or with primary diagnosis of idiopathic dilated cardiomyopathy is large and exceeds the initially planned 33% mortality reduction. The *P* value achieved when survival curves are compared using the log-rank test is .01. In some previous studies where both ischemic and nonischemic patients were included, functional and hemodynamic improvement with β-blockade was greater in nonischemic patients than in ischemic patients. This was observed with bucindolol[18] and with metoprolol.[16,19] Beneficial antiarrhythmic effects in patients with heart failure, history of myocardial infarction, and life-threatening ventricular arrhythmias have been suggested by nonrandomized studies.[20,21] However, no previous studies have been large enough to determine whether there is a difference between nonischemic and ischemic patients. Because in CIBIS an enhanced effect on survival was observed in patients without a history of myocardial infarction and because by chance significantly more patients with a history of myocardial infarction were included in the bisoprolol group (Table 1), this should have reduced the overall effect of bisoprolol on mortality. However, such an unbalanced distribution by etiology was unlikely to have altered the result over the entire population, although it may have contributed to a reduction in the ability of the study to show an effect.

There is no clear explanation for such a suggested differential effect of β-blockade related to etiology. On the contrary, one might have anticipated cardioprotection following ischemic β-blockade in ischemic patients. After myocardial infarction, β-blockade therapy has largely proven to be beneficial with a 20% to 25% reduction in 1-year mortality (especially sudden death) and in nonfatal myocardial reinfarction rate.[22-24] In addition, benefit appears to be greater in high-risk patients with large infarct size and low ejection fraction.[24]

The mechanisms of protection afforded by β-blockade in chronic heart failure patients thus could differ from that observed after a myocardial infarction where acute coronary thrombosis and fatal ventricular arrhythmias appear to be prevented by β-blockade, which could explain the reduction in sudden death rate with β-blockers for the latter indication.

Whatever the etiology, the mechanism of β-blockade–induced benefit in heart failure remains to be clarified. Several hypotheses have been proposed to explain such an improvement.[6,25] High sympathetic stimulation that progressively increases with heart fail-

ure development could accelerate left ventricular dysfunction by increasing oxygen consumption and subendocardial ischemia in these dilated and energy-depleted hearts. Preventing such an adrenergic cardiac toxicity with β-blocking agents thus should be beneficial.

However, conversely, sympathetic stimulation leads to β-adrenergic receptor desensitization,[24,27] which is associated with a reduction in inotropic response to β-agonist stimulation.

In addition, different intensities of β-adrenergic receptor desensitization and uncoupling with adenyl cyclase in ischemic and nonischemic cardiomyopathy has been demonstrated by Bristow et al.[26] Whether this loss of adrenergic reactivity plays a role during heart failure deterioration is unknown. Such differences in β receptor behavior according to etiology could potentially influence β-blocker effects, but this remains to be investigated.

Indeed, β-blockade treatment has been shown to increase β-adrenergic receptor number and to enhance β_1-adrenergic receptor sensitivity in heart failure due to idiopathic dilated cardiomyopathy.[28] This effect cannot directly explain improvement if one considers that sympathetic cardiac toxicity plays a direct deleterious role. β-Adrenergic receptor upregulation during β-blocker therapy is not necessary for improved left ventricular function in heart failure.[29] However, even with improved sensitivity to β stimulation, continued β-blockade will prevent acute peaks of norepinephrine stimulation.

β-Blockade–induced bradycardia per se could play a key role since heart failure can be experimentally induced by chronic rapid cardiac pacing in rat or dogs.[30]

In conclusion, CIBIS results demonstrate that β-blockade with bisoprolol, when cautiously administered to patients with heart failure using a progressive dose-increment schedule, is well tolerated and can reduce the rate of deterioration episodes requiring hospitalization.

Other trials are mandatory to prove a beneficial effect on mortality. It may be wise to stratify patients according to etiology, especially according to history of myocardial infarction, in future trials.

Appendix

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